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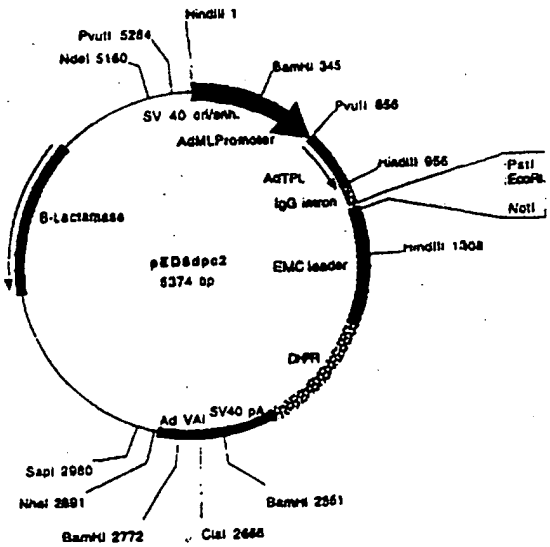
(54) Title: SECRETED PROTEINS

(57) Abstract

Novel proteins are disclosed.




Plasmid name: pED6dpc2
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. EST cDNAs are cloned between EcoRI and NotI
[illegible] et al (1991). NAR 19: 4485-4490.

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# SECRETED PROTEINS

## FIELD OF THE INVENTION

The present invention provides novel proteins , along with therapeutic, diagnostic and research utilities for these proteins.

## BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins that the present invention is directed.

## SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 28 to nucleotide 276;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AE402_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AE402_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AE402_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AE402_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 28 to nucleotide 276; the nucleotide sequence of the full length protein coding sequence of clone AE402_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone AE402_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AE402_1i deposited under accession number ATCC 98190.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) fragments of the amino acid sequence of SEQ ID NO:2; and

(c) the amino acid sequence encoded by the cDNA insert of clone AE402_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:2.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:4;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:4 from nucleotide 61 to nucleotide 513;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:4 from nucleotide 322 to nucleotide 513;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AE610_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AE610_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AE610_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AE610_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:5;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:5 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:4 from nucleotide 61 to nucleotide 513; the nucleotide sequence of SEQ ID NO:4 from nucleotide 322 to nucleotide 513; the nucleotide sequence of the full length protein coding sequence of clone AE610_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone AE610_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AE610_1i deposited under accession number ATCC 98190.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:5;

(b) fragments of the amino acid sequence of SEQ ID NO:5; and

(c) the amino acid sequence encoded by the cDNA insert of clone AE610_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:5.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 20 to nucleotide 523;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AH106_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AH106_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AH106_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AH106_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:7 from nucleotide 20 to nucleotide 523; the nucleotide sequence of the full length protein coding sequence of clone AH106_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone AH106_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AH106_1i deposited under accession number ATCC 98190.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) fragments of the amino acid sequence of SEQ ID NO:8; and

(c) the amino acid sequence encoded by the cDNA insert of clone AH106_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:8.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 130 to nucleotide 309;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AH196_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AH196_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AH196_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AH196_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 130 to nucleotide 309; the nucleotide sequence of the full length protein

coding sequence of clone AH196_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone AH196_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AH196_1i deposited under accession number ATCC 98190.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) fragments of the amino acid sequence of SEQ ID NO:10; and

(c) the amino acid sequence encoded by the cDNA insert of clone AH196_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:10.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12 from nucleotide 69 to nucleotide 467;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AI6_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AI6_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AI6_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AI6_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:13;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:13 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:12 from nucleotide 69 to nucleotide 467; the nucleotide sequence of the full length protein coding sequence of clone AI6_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone AI6_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AI6_1i deposited under accession number ATCC 98190. In yet other preferred embodiments, such polynucleotide encodes a protein comprising the amino acid sequence of SEQ ID NO:13 from amino acid 69 to amino acid 133.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:13;

(b) the amino acid sequence of SEQ ID NO:13 from amino acid 69 to amino acid 133;

(c) fragments of the amino acid sequence of SEQ ID NO:13; and

(d) the amino acid sequence encoded by the cDNA insert of clone AI6_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:13 or the amino acid sequence of SEQ ID NO:13 from amino acid 69 to amino acid 133.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:16;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:16 from nucleotide 55 to nucleotide 337;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AJ13_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AJ13_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ13_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ13_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:17;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:17 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:16 from nucleotide 55 to nucleotide 337; the nucleotide sequence of the full length protein coding sequence of clone AJ13_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone AJ13_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AJ13_1i deposited under accession number ATCC 98190. In yet other preferred embodiments, such polynucleotide encodes a protein comprising the amino acid sequence of SEQ ID NO:17 from amino acid 12 to amino acid 94.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:17;

(b) the amino acid sequence of SEQ ID NO:17 from amino acid 12 to amino acid 94;

(c) fragments of the amino acid sequence of SEQ ID NO:17; and

(d) the amino acid sequence encoded by the cDNA insert of clone AJ13_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:17 or the amino acid sequence of SEQ ID NO:17 from amino acid 12 to amino acid 94.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 33 to nucleotide 422;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 114 to nucleotide 422;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AJ27_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AJ27_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ27_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ27_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:19 from nucleotide 33 to nucleotide 422; the nucleotide sequence of SEQ ID NO:19 from nucleotide 114 to nucleotide 422; the nucleotide sequence of the full length protein coding sequence of clone AJ27_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone AJ27_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full

length or mature protein encoded by the cDNA insert of clone AJ27_1i deposited under accession number ATCC 98190.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:20;

(b) fragments of the amino acid sequence of SEQ ID NO:20; and

(c) the amino acid sequence encoded by the cDNA insert of clone AJ27_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:20.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:22;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:22 from nucleotide 47 to nucleotide 517;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:22 from nucleotide 116 to nucleotide 517;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AJ142_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AJ142_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ142_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ142_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:23;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:23 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:22 from nucleotide 47 to nucleotide 517; the nucleotide sequence of SEQ ID NO:22 from nucleotide 116 to nucleotide 517; the nucleotide sequence of the full length protein coding sequence of clone AJ142_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone AJ142_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AJ142_1i deposited under accession number ATCC 98190.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:23;

(b) fragments of the amino acid sequence of SEQ ID NO:23; and

(c) the amino acid sequence encoded by the cDNA insert of clone AJ142_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:23.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:24;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:24 from nucleotide 312 to nucleotide 417;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AK604_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AK604_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AK604_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AK604_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:25;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:25 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:24 from nucleotide 312 to nucleotide 417; the nucleotide sequence of the full length protein coding sequence of clone AK604_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone AK604_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AK604_1i deposited under accession number ATCC 98190.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:25;

(b) fragments of the amino acid sequence of SEQ ID NO:25; and

(c) the amino acid sequence encoded by the cDNA insert of clone AK604_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:25.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 76 to nucleotide 372;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AK620_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AK620_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AK620_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AK620_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:28;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:28 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:27 from nucleotide 76 to nucleotide 372; the nucleotide sequence of the full length protein coding sequence of clone AK620_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone AK620_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AK620_1i deposited under accession number ATCC 98190.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:28;

(b) fragments of the amino acid sequence of SEQ ID NO:28; and

(c) the amino acid sequence encoded by the cDNA insert of clone AK620_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:28.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:29;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:29 from nucleotide 367 to nucleotide 552;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AK650_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AK650_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AK650_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AK650_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:30;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:30 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:29 from nucleotide 367 to nucleotide 552; the nucleotide sequence of the full length protein coding sequence of clone AK650_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone AK650_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AK650_1i deposited under accession number ATCC 98190.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:30;

(b) fragments of the amino acid sequence of SEQ ID NO:30; and

(c) the amino acid sequence encoded by the cDNA insert of clone AK650_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:30.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 116 to nucleotide 310;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 173 to nucleotide 310;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AM226_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AM226_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AM226_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AM226_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:33;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:33 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:32 from nucleotide 116 to nucleotide 310; the nucleotide sequence of SEQ ID NO:32 from nucleotide 173 to nucleotide 310; the nucleotide sequence of the full length protein coding sequence of clone AM226_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone AM226_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AM226_1i deposited under accession number ATCC 98190.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:33;

(b) fragments of the amino acid sequence of SEQ ID NO:33; and

(c) the amino acid sequence encoded by the cDNA insert of clone AM226_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:33.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:35;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:35 from nucleotide 281 to nucleotide 418;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:35 from nucleotide 353 to nucleotide 418;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AR417_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AR417_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AR417_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AR417_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:36;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:36 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:35 from nucleotide 281 to nucleotide 418; the nucleotide sequence of SEQ ID NO:35 from nucleotide 353 to nucleotide 418; the nucleotide sequence of the full length protein coding sequence of clone AR417_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone AR417_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AR417_1i deposited under accession number ATCC 98190.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:36;

(b) fragments of the amino acid sequence of SEQ ID NO:36; and

(c) the amino acid sequence encoded by the cDNA insert of clone AR417_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:36.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:38;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:38 from nucleotide 496 to nucleotide 583;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:38 from nucleotide 565 to nucleotide 583;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AU43_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AU43_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AU43_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AU43_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:39;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:39 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:38 from nucleotide 496 to nucleotide 583; the nucleotide sequence of SEQ ID NO:38 from nucleotide 565 to nucleotide 583; the nucleotide sequence of the full length protein coding sequence of clone AU43_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone AU43_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AU43_1i deposited under accession number ATCC 98190.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:39;

(b) fragments of the amino acid sequence of SEQ ID NO:39; and

(c) the amino acid sequence encoded by the cDNA insert of clone AU43_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:39.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:41;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:41 from nucleotide 55 to nucleotide 405;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:41 from nucleotide 148 to nucleotide 405;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AW60_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AW60_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AW60_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AW60_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:42;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:42 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:41 from nucleotide 55 to nucleotide 405; the nucleotide sequence of SEQ ID NO:41 from nucleotide 148 to nucleotide 405; the nucleotide sequence of the full length protein coding sequence of clone AW60_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone AW60_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone AW60_1i deposited under accession number ATCC 98190.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:42;

(b) fragments of the amino acid sequence of SEQ ID NO:42; and

(c) the amino acid sequence encoded by the cDNA insert of clone AW60_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:42.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:44;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:44 from nucleotide 337 to nucleotide 525;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:44 from nucleotide 406 to nucleotide 525;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BA176_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BA176_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BA176_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BA176_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:45;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:45 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:44 from nucleotide 337 to nucleotide 525; the nucleotide sequence of SEQ ID NO:44 from nucleotide 406 to nucleotide 525; the nucleotide sequence of the full length protein coding sequence of clone BA176_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone BA176_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone BA176_1i deposited under accession number ATCC 98190.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:45;

(b) fragments of the amino acid sequence of SEQ ID NO:45; and

(c) the amino acid sequence encoded by the cDNA insert of clone BA176_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:45.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:47;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:47 from nucleotide 536 to nucleotide 628;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BD140_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BD140_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BD140_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BD140_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:48;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:48 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:47 from nucleotide 536 to nucleotide 628; the nucleotide sequence of the full length protein

coding sequence of clone BD140_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone BD140_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone BD140_1i deposited under accession number ATCC 98190.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:48;

(b) fragments of the amino acid sequence of SEQ ID NO:48; and

(c) the amino acid sequence encoded by the cDNA insert of clone BD140_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:48.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:50;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:50 from nucleotide 303 to nucleotide 617;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:50 from nucleotide 345 to nucleotide 617;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BD407_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BD407_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BD407_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BD407_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:51;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:51 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:50 from nucleotide 303 to nucleotide 617; the nucleotide sequence of SEQ ID NO:50 from nucleotide 345 to nucleotide 617; the nucleotide sequence of the full length protein coding sequence of clone BD407_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone BD407_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone BD407_1i deposited under accession number ATCC 98190. In yet other preferred embodiments, such polynucleotide encodes a protein comprising the amino acid sequence of SEQ ID NO:51 from amino acid 1 to amino acid 32.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:51;

(b) the amino acid sequence of SEQ ID NO:51 from amino acid 1 to amino acid 32;

(c) fragments of the amino acid sequence of SEQ ID NO:51; and

(d) the amino acid sequence encoded by the cDNA insert of clone BD407_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:51 or the amino acid sequence of SEQ ID NO:51 from amino acid 1 to amino acid 32.

In one embodiment, the present invention provides a composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:52;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:52 from nucleotide 178 to nucleotide 534;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BF290_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BF290_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BF290_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BF290_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:53;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:53 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:52 from nucleotide 178 to nucleotide 534; the nucleotide sequence of the full length protein coding sequence of clone BF290_1i deposited under accession number ATCC 98190; or the nucleotide sequence of the mature protein coding sequence of clone BF290_1i deposited under accession number ATCC 98190. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone BF290_1i deposited under accession number ATCC 98190.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:53;

(b) fragments of the amino acid sequence of SEQ ID NO:53; and

(c) the amino acid sequence encoded by the cDNA insert of clone BF290_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:53.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

## BRIEF DESCRIPTION OF FIGURES

Fig. 1 is a schematic representation of the pED6 and pNotS vectors used for deposit of clones disclosed herein.

Fig. 2 is an autoradiograph evidencing the expression of the following clone(s) disclosed herein: AE610_1i.

Fig. 3 is an autoradiograph evidencing the expression of the following clone(s) disclosed herein: AH106_1i, AM226_1i.

Fig. 4 is an autoradiograph evidencing the expression of the following clone(s) disclosed herein: AH196_1i.

Fig. 5 is an autoradiograph evidencing the expression of the following clone(s) disclosed herein: AI6_1i.

Fig. 6 is an autoradiograph evidencing the expression of the following clone(s) disclosed herein: AR417_1i.

Fig. 7 is an autoradiograph evidencing the expression of the following clone(s) disclosed herein: AW60_1i.

Fig. 8 is an autoradiograph evidencing the expression of the following clone(s) disclosed herein: BD140_1i.

Fig. 9 is an autoradiograph evidencing the expression of the following clone(s) disclosed herein: BF290_1i.

## DETAILED DESCRIPTION

### ISOLATED PROTEINS

Nucleotide and amino acid sequences are reported below for each clone and protein disclosed in the present application. In some instances the sequences are preliminary and may include some incorrect or ambiguous bases or amino acids. The actual nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full length and mature) can

then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence.

For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing. Because of the partial ambiguity in reported sequence information, reported protein sequences include "Xaa" designators. These "Xaa" designators indicate either (1) a residue which cannot be identified because of nucleotide sequence ambiguity or (2) a stop codon in the determined nucleotide sequence where applicants believe one should not exist (if the nucleotide sequence were determined more accurately).

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g. , receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplpasmic reticulum.

Protein "AE402_1i"

One protein of the present invention has been identified as protein "AE402_1i". A partial cDNA clone encoding AE402_1i was first isolated from a murine adult spleen cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with ESTs reported by the I.M.A.G.E. Consortium identified as "yh02h12.r1 Homo sapiens cDNA clone 42238 5'" (R60758, BlastN) and "yh02h12.s1 Homo sapiens cDNA clone 42238 3'" (R60759, BlastN). The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "AE402_1i".

Applicants' methods identified clone AE402_1i as encoding a secreted protein.

The nucleotide sequence of the 5' portion of AE402_1i as presently determined is reported in SEQ ID NO:1. What applicants believe is the proper reading frame and the predicted amino acid sequence of the AE402_1i protein corresponding to the foregoing

nucleotide sequence is reported in SEQ ID NO:2. Additional nucleotide sequence from the 3' portion of AE402_1i, including the polyA tail, is reported in SEQ ID NO:3.

Protein "AE610_1i"

One protein of the present invention has been identified as protein "AE610_1i". A partial cDNA clone encoding AE610_1i was first isolated from a murine adult spleen cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with ESTs reported by the I.M.A.G.E. Consortium identified as "yf19g02.r1 Homo sapiens cDNA" (R08399, Fasta), "yw68d09.s1 Homo sapiens cDNA clone 257393 3'" (N27174, BlastN), "yi10a04.r1 Homo sapiens cDNA" (R62698, Fasta) and "yh78e10.s1 Homo sapiens cDNA clone 135882 3'" (R33815, BlastN). The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "AE610_1i".

Applicants' methods identified clone AE610_1i as encoding a secreted protein.

The nucleotide sequence of the 5' portion of AE610_1i as presently determined is reported in SEQ ID NO:4. What applicants believe is the proper reading frame and the predicted amino acid sequence of the AE610_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:5. Amino acids 1 to 87 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 88. Additional nucleotide sequence from the 3' portion of AE610_1i, including the polyA tail. is reported in SEQ ID NO:6.

Protein "AH106_1i"

One protein of the present invention has been identified as protein "AH106_1i". A partial cDNA clone encoding AH106_1i was first isolated from a murine fetal thymus cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with an EST reported by the I.M.A.G.E. Consortium identified at GenBank accession number T81127. The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E.

Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "AH106_1i".

Applicants' methods identified clone AH106_1i as encoding a secreted protein.

The nucleotide sequence of AH106_1i as presently determined is reported in SEQ ID NO:7. What applicants believe is the proper reading frame and the predicted amino acid sequence of the AH106_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:8..

Protein "AH196_1i"

One protein of the present invention has been identified as protein "AH196_1i". A partial cDNA clone encoding AH196_1i was first isolated from a murine fetal thymus cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with ESTs reported by the I.M.A.G.E. Consortium identified as "yj12f04.r1 Homo sapiens cDNA clone 148543 5'" (H12523, BlastN) and "yj12f04.s1 Homo sapiens cDNA clone 148543 3'" (H12470, BlastN). The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "AH196_1i".

Applicants' methods identified clone AH196_1i as encoding a secreted protein.

The nucleotide sequence of the 5' portion of AH196_1i as presently determined is reported in SEQ ID NO:9. What applicants believe is the proper reading frame and the predicted amino acid sequence of the AH196_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:10. Additional nucleotide sequence from the 3' portion of AH196_1i, including the polyA tail, is reported in SEQ ID NO:11.

Protein "AI6_1i"

One protein of the present invention has been identified as protein "AI6_1i". A partial cDNA clone encoding AI6_1i was first isolated from a human blood cell (Th1 or Th2) cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least

some identity with ESTs reported by the I.M.A.G.E. Consortium identified as "yj42h04.r1 Homo sapiens cDNA" (H03613, Fasta) and "yx60f10.s1 Homo sapiens cDNA clone 266155 3'" (N21637, BlastN). The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "AI6_1i".

Applicants' methods identified clone AI6_1i as encoding a secreted protein.

The nucleotide sequence of the 5' portion of AI6_1i as presently determined is reported in SEQ ID NO:12. What applicants believe is the proper reading frame and the predicted amino acid sequence of the AI6_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:13. Additional nucleotide sequence from the 3' portion of AI6_1i, including the polyA tail, is reported in SEQ ID NO:14.

Protein "AJ13_1i"

One protein of the present invention has been identified as protein "AJ13_1i". A partial cDNA clone encoding AJ13_1i was first isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with ESTs reported by the I.M.A.G.E. Consortium identified as "yo61h02.r1 Homo sapiens cDNA clone 182451 5'" (H42116, BlastN), "yr84a08.r1 Homo sapiens cDNA clone 211958 5'" (H75363, BlastN) and "yg83h03.s1 Homo sapiens cDNA clone 40148 3'" (R53978, BlastN). The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "AJ13_1i".

Applicants' methods identified clone AJ13_1i as encoding a secreted protein.

The nucleotide sequence of the 5' portion of AJ13_1i as presently determined is reported in SEQ ID NO:15. An additional internal nucleotide sequence from AJ13_1i as presently determined is reported in SEQ ID NO:16. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:17. Additional nucleotide sequence from the 3' portion of AJ13_1i, including the polyA tail, is reported in SEQ ID NO:18.

Protein "AJ27_1i"

One protein of the present invention has been identified as protein "AJ27_1i". A partial cDNA clone encoding AJ27_1i was first isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with ESTs reported by the I.M.A.G.E. Consortium identified as "yx25h01.r1 Homo sapiens cDNA clone 262897 5'" (N28373, BlastN) and "yx62d05.r1 Homo sapiens cDNA clone 266313 5'" (N35654, BlastN). The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "AJ27_1i".

Applicants' methods identified clone AJ27_1i as encoding a secreted protein.

The nucleotide sequence of the 5' portion of AJ27_1i as presently determined is reported in SEQ ID NO:19. What applicants believe is the proper reading frame and the predicted amino acid sequence of the AJ27_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:20. Amino acids 1 to 27 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 28. Additional nucleotide sequence from the 3' portion of AJ27_1i, including the polyA tail, is reported in SEQ ID NO:21.

Protein "AJ142_1i"

One protein of the present invention has been identified as protein "AJ142_1i". A partial cDNA clone encoding AJ142_1i was first isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with ESTs reported by the I.M.A.G.E. Consortium identified as "yq85b12.r1 Homo sapiens cDNA clone 202559 5'" (H53268, BlastN) and "yq85b12.s1 Homo sapiens cDNA clone 202559 3'" (H53269, BlastN). The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "AJ142_1i".

Applicants' methods identified clone AJ142_1i as encoding a secreted protein.

The nucleotide sequence of AJ142_1i as presently determined is reported in SEQ ID NO:22. What applicants believe is the proper reading frame and the predicted amino acid sequence of the AJ142_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:23. Amino acids 1 to 23 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 24.

Protein "AK604_1i"

One protein of the present invention has been identified as protein "AK604_1i". A partial cDNA clone encoding AK604_1i was first isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with an EST reported by the I.M.A.G.E. Consortium identified as "yc80g11.r1 Homo sapiens cDNA clone 22157 5'" (T64857, BlastN). The sequence also showed at least some identity with a partial cDNA sequence identified as "H. sapiens partial cDNA sequence; clone c-1pg11" (Z40033, BlastN). The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "AK604_1i".

Applicants' methods identified clone AK604_1i as encoding a secreted protein.

The nucleotide sequence of the 5' portion of AK604_1i as presently determined is reported in SEQ ID NO:24. What applicants believe is the proper reading frame and the predicted amino acid sequence of the AK604_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:25. Additional nucleotide sequence from the 3' portion of AK604_1i, including the polyA tail, is reported in SEQ ID NO:26.

Protein "AK620_1i"

One protein of the present invention has been identified as protein "AK620_1i". A partial cDNA clone encoding AK620_1i was first isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with ESTs reported by the I.M.A.G.E. Consortium identified as "ye7607.r1

Homo sapiens cDNA clone 123684 5'" (R02637, BlastN) and "yx90e05.s1 Homo sapiens cDNA clone 269024 3'" (N26101, BlastN). The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "AK620_1i".

Applicants' methods identified clone AK620_1i as encoding a secreted protein.

The nucleotide sequence of AK620_1i as presently determined is reported in SEQ ID NO:27. What applicants believe is the proper reading frame and the predicted amino acid sequence of the AK620_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:28..

Protein "AK650_1i"

One protein of the present invention has been identified as protein "AK650_1i". A partial cDNA clone encoding AK650_1i was first isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with ESTs reported by the I.M.A.G.E. Consortium identified as "yp60g06.r1 Homo sapiens cDNA clone 191866 5'" (H40407, BlastN) and "yp60g06.s1 Homo sapiens cDNA clone 191866 3'" (H40350, BlastN). The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "AK650_1i".

Applicants' methods identified clone AK650_1i as encoding a secreted protein.

The nucleotide sequence of the 5' portion of AK650_1i as presently determined is reported in SEQ ID NO:29. What applicants believe is the proper reading frame and the predicted amino acid sequence of the AK650_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:30. Additional nucleotide sequence from the 3' portion of AK650_1i, including the polyA tail, is reported in SEQ ID NO:31.

Protein "AM226_1i"

One protein of the present invention has been identified as protein "AM226_1i". A partial cDNA clone encoding AM226_1i was first isolated from a human fetal kidney cDNA

library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with ESTs reported by the I.M.A.G.E. Consortium identified as "yf09a01.r1 Homo sapiens cDNA clone 126312 5'" (R06469, BlastN) and "yy49b06.s1 Homo sapiens cDNA clone 276851 3'" (N39415, BlastN). The sequence also showed some similarity with bovine osteoinductuve factor (OIF) (M37974, BlastN), with which it may share some activity. The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "AM226_1i".

Applicants' methods identified clone AM226_1i as encoding a secreted protein.

The nucleotide sequence of the 5' portion of AM226_1i as presently determined is reported in SEQ ID NO:32. What applicants believe is the proper reading frame and the predicted amino acid sequence of the AM226_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:33. Amino acids 1 to 19 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 20. Additional nucleotide sequence from the 3' portion of AM226_1i, including the polyA tail, is reported in SEQ ID NO:34.

Protein "AR417_1i"

One protein of the present invention has been identified as protein "AR417_1i". A partial cDNA clone encoding AR417_1i was first isolated from a human adult retina cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with ESTs reported by the I.M.A.G.E. Consortium identified at GenBank accession numbers R18973, R42209 ("yf89g09.s1 Homo sapiens cDNA clone 29781 3'"), R12416 ("yf56a02.r1 Homo sapiens cDNA clone 26106 5'") and R15309 ("yf89g09.r1 Homo sapiens cDNA"). The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "AR417_1i".

Applicants' methods identified clone AR417_1i as encoding a secreted protein.

The nucleotide sequence of the 5' portion of AR417_1i as presently determined is reported in SEQ ID NO:35. What applicants believe is the proper reading frame and the predicted amino acid sequence of the AR417_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:36. Amino acids 1 to 24 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 25. Additional nucleotide sequence from the 3' portion of AR417_1i, including the polyA tail, is reported in SEQ ID NO:37.

Protein "AU43_1i"

One protein of the present invention has been identified as protein "AU43_1i". A partial cDNA clone encoding AU43_1i was first isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with ESTs reported by the I.M.A.G.E. Consortium identified as "yi49f07.r1 Homo sapiens cDNA clone 142597 5'" (R70850, BlastN) and "yd68e02.s1 Homo sapiens cDNA clone 113402 3'" (T78464, BlastN). The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "AU43_1i".

Applicants' methods identified clone AU43_1i as encoding a secreted protein.

The nucleotide sequence of the 5' portion of AU43_1i as presently determined is reported in SEQ ID NO:38. What applicants believe is the proper reading frame and the predicted amino acid sequence of the AU43_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:39. Amino acids 1 to 23 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 24. Additional nucleotide sequence from the 3' portion of AU43_1i, including the polyA tail, is reported in SEQ ID NO:40.

Protein "AW60_1i"

One protein of the present invention has been identified as protein "AW60_1i". A partial cDNA clone encoding AW60_1i was first isolated from a human ovary (PA-1 teratocarcinoma) cDNA library using methods which are selective for cDNAs encoding

secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with ESTs reported by the I.M.A.G.E. Consortium identified as "ym57f11.r1 Homo sapiens cDNA clone 52343 5'" (H23492, BlastN), "ym57f08.r1 Homo sapiens cDNA" (H23390, Fasta) and "ym57f11.s1 Homo sapiens cDNA clone 52343 3'" (H23494, BlastN). The sequence also showed at least some identity with a sequence identified as "Homo sapiens clone S31i125" (L40397, Fasta)The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "AW60_1i".

Applicants' methods identified clone AW60_1i as encoding a secreted protein.

The nucleotide sequence of the 5' portion of AW60_1i as presently determined is reported in SEQ ID NO:41. What applicants believe is the proper reading frame and the predicted amino acid sequence of the AW60_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:42. Amino acids 1 to 31 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 32. Additional nucleotide sequence from the 3' portion of AW60_1i, including the polyA tail, is reported in SEQ ID NO:43.

Protein "BA176_1i"

One protein of the present invention has been identified as protein "BA176_1i". A partial cDNA clone encoding BA176_1i was first isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with ESTs reported by the I.M.A.G.E. Consortium identified as "yi75g11.r1 Homo sapiens cDNA" (R77409, Fasta), "yj50b12.r1 Homo sapiens cDNA" (H03089, Fasta) and "yi75g11.s1 Homo sapiens cDNA clone 145124 3'" (R77410, BlastN). The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "BA176_1i".

Applicants' methods identified clone BA176_1i as encoding a secreted protein.

The nucleotide sequence of the 5' portion of BA176_1i as presently determined is reported in SEQ ID NO:44. What applicants believe is the proper reading frame and the predicted amino acid sequence of the BA176_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:45. Amino acids 1 to 23 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 24. Additional nucleotide sequence from the 3' portion of BA176_1i, including the polyA tail, is reported in SEQ ID NO:46.

Protein "BD140_1i"

One protein of the present invention has been identified as protein "BD140_1i". A partial cDNA clone encoding BD140_1i was first isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with ESTs reported by the I.M.A.G.E. Consortium identified as "yn98c02.r1 Homo sapiens cDNA" (H43507, Fasta), "yn67g04.r1 Homo sapiens cDNA" (H22693, Fasta) and "yn82e07.s1 Homo sapiens cDNA clone 174948 3'" (H38408, BlastN). The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "BD140_1i".

Applicants' methods identified clone BD140_1i as encoding a secreted protein.

The nucleotide sequence of the 5' portion of BD140_1i as presently determined is reported in SEQ ID NO:47. What applicants believe is the proper reading frame and the predicted amino acid sequence of the BD140_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:48. Additional nucleotide sequence from the 3' portion of BD140_1i, including the polyA tail, is reported in SEQ ID NO:49.

Protein "BD407_1i"

One protein of the present invention has been identified as protein "BD407_1i". A partial cDNA clone encoding BD407_1i was first isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with ESTs reported by the I.M.A.G.E. Consortium identified as "ys65a05.r1

Homo sapiens cDNA" (H84524, Fasta) and "yz15h02.s1 Homo sapiens cDNA clone 283155 3'" (N51349, BlastN). The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "BD407_1i".

Applicants' methods identified clone BD407_1i as encoding a secreted protein.

The nucleotide sequence of BD407_1i as presently determined is reported in SEQ ID NO:50. What applicants believe is the proper reading frame and the predicted amino acid sequence of the BD407_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:51. Amino acids 1 to 14 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 15.

Protein "BF290_1i"

One protein of the present invention has been identified as protein "BF290_1i". A partial cDNA clone encoding BF290_1i was first isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins. The nucleotide sequence of such partial cDNA was determined and searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The search revealed at least some identity with ESTs reported by the I.M.A.G.E. Consortium identified as "yh10f04.r1 Homo sapiens cDNA" (R61165, Fasta) and "yy35d12.s1 Homo sapiens cDNA clone 273239 3'" (N33175, BlastN). The human cDNA clone corresponding to the EST database entry was ordered from Genome Systems, Inc., St. Louis, Mo, a distributor of the I.M.A.G.E. Consoritum library. The clone received from the distributor was examined and determined to be a full length clone, including a 5' end and 3' UTR (including a polyA tail). This full-length clone is also referred to herein as "BF290_1i".

Applicants' methods identified clone BF290_1i as encoding a secreted protein.

The nucleotide sequence of the 5' portion of BF290_1i as presently determined is reported in SEQ ID NO:52. What applicants believe is the proper reading frame and the predicted amino acid sequence of the BF290_1i protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:53. Additional nucleotide sequence from the 3' portion of BF290_1i, including the polyA tail, is reported in SEQ ID NO:54.

Deposit of Clones

Clones AE402_1i, AE610_1i, AH106_1i, AH196_1i, AI6_1i, AJ13_1i, AJ27_1i, AJ142_1i, AK604_1i, AK620_1i, AK650_1i, AM226_1i, AR417_1i, AU43_1i, AW60_1i, BA176_1i, BD140_1i, BD407_1i and BF290_1i were deposited on October 2, 1996 with the American Type Culture Collection under accession number ATCC 98190, from which each clone comprising a particular polynucleotide is obtainable. Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit.

Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' cite, EcoRI; 3' cite, NotI) to produce the appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNotS vector depicted in Fig. 1. In some instances, the deposited clone can become "flipped" (i.e., in the reverse orientation) in the deposited isolate. In such instances, the cDNA insert can still be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' cite and EcoRI will produce the 3' cite for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the vectors in which they were deposited.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences.

In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoaramidite residue rather than a nucleotide (such as , for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramadite) (Glen Research, cat. no. 10-1953)).

The design of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) It should be designed to have a $T_m$ of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with g-$^{32}$P ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in

a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 µg/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100 µg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 µg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an

immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein may also be determinable from the amino acid sequence of the full-length form.

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Species homologs of the disclosed proteins are also provided by the present invention. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed proteins; that is, naturally-occurring alternative forms of the isolated proteins which are identical, homologous or related to that encoded by the polynucleotides disclosed herein.

The isolated polynucleotide endcoing the protein of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces* strains, *Candida,* or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli, Bacillus subtilis, Salmonella typhimurium,* or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits

for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

## USES AND BIOLOGICAL ACTIVITY

The proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

### Research Uses and Utilities

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria

spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without

transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science *257*:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, *89*:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting

an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I $\alpha$ chain protein and $\beta_2$ microglobulin protein or an MHC class II $\alpha$ chain protein and an MHC class II $\beta$ chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*, B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally,

a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeck, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in:

Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell

disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 1-21, Wiley-Liss, Inc.., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation

employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically,

a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium ).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be

readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell

interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

## ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical

composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunolgobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the pres nt invention is combined, in addition to other pharmaceutically

acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition

of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 µg to about 100 mg (preferably about 0.1µg to about 10 mg, more preferably about 0.1 µg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated

that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular

application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorbtion of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

SEQUENCE LISTING

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(ii) TITLE OF INVENTION: SECRETED PROTEINS

(iii) NUMBER OF SEQUENCES: 54

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(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 276 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

AAGCTTGGGG TTTTCTGGGC TACTACGATG GCGATGAGTT TCGAGTGGCC GTGGCAGTAC 60

CGCTTCCCGC CCTTCTTTAC GTTACAGCCG AACGTGGACA CCCGGCAGAA GCAGCTGGCC 120

GCCTGGTGCT CTCTGGTTCT GTCCTTCTGC CGCCTGCACA AACAGTCCAG CATGACGGTG 180

ATGGAAGCCC AGGAGAGCCC GCTTTTCAAC AACGTCAAGC TACAGCGGAA ACTTCCTGTG 240

GAGTCAATTC AGATTGTATT AGAAGAACTG AGAAAG 276

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 83 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Ala Met Ser Phe Glu Trp Pro Trp Gln Tyr Arg Phe Pro Pro Phe
1 5 10 15

Phe Thr Leu Gln Pro Asn Val Asp Thr Arg Gln Lys Gln Leu Ala Ala
20 25 30

Trp Cys Ser Leu Val Leu Ser Phe Cys Arg Leu His Lys Gln Ser Ser
35 40 45

Met Thr Val Met Glu Ala Gln Glu Ser Pro Leu Phe Asn Asn Val Lys
50 55 60

Leu Gln Arg Lys Leu Pro Val Glu Ser Ile Gln Ile Val Leu Glu Glu
65 70 75 80

Leu Arg Lys

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 246 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

GTGAGTACAT ACACACANGC GCNTGCAGCA CANGATTNTG TCTCATCGTC NTCCCACCCN 60

NNNNGGNGNN GNTGCCTCCC TTAGTCAGGN GANGATGNAT CCTTTCCNAG GGGNTGGGGG 120

GNANCATTGG ATGCGGGCAG CNTTCCAGGC AANATGAAGA TNGGAGGCCC ACGGGCATGG 180

CAGTGAGAGG NGTGGCCCCA CACNGATTTA TGATNTTGAA ATCTCAACTC CCAAAAAAGA 240

AAAAAA 246

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 632 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

AGCTTCGGAA TAATAATTTT GGCAAATCTA TCTTCTGAAC CACTCATTTC TGTGGTCTTA 60

ATGGCTCCAA TTTGGGGACC AATAATGTTC ATTGTCTCAG GATCCCTGTC AATTGCAGCA 120

GGAGTGAAAC CTACAAAAAG CCTGATCATC AGCAGTCTAA CTCTGAACAC TATCACCTCT 180

GTGTTGGCTG CAACTGCAAG CATAATGGGT GTAGTCAGTG TGGCTGTGGG TTCACAGTTT 240

CCGTTTCGGT ATAATTATAC AATCACCAAG GGTTTGGATA TTTTGATGTT AATTTTAAAT 300

ATGCTAGAAT TCTGCATTGC TGTGTCCATC TCTGCTTTTG GATGTAAAGC TTCCTGTTGT 360

AACTCCAGCG AGGTTCTTGT AGTGCTACCA TCAAATCCTG CTGTGACTGT GATGGCACCC 420

CCCACACCAC TTAATGAAGG TTTGAGGCCA CCAAAAGATC AACAGACAAA TGCTCCAGAA 480

ATCTATGCTG ACTGTGACAC AAGAAGCCTC ACATGAAGAA ATTACCAGTA TCCAACTTCG 540

ATACTGATAG ACTTGTTGAT ATTATTATTA TATGTAATCC AATTATGAAC TGTGTGTGTA 600

TAGAGAGATA ATAAATTCAA AATTATGTTC TC 632

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 151 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

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Met Ala Pro Ile Trp Gly Pro Ile Met Phe Ile Val Ser Gly Ser Leu
1               5                  10                  15

Ser Ile Ala Ala Gly Val Lys Pro Thr Lys Ser Leu Ile Ile Ser Ser
            20                  25                  30

Leu Thr Leu Asn Thr Ile Thr Ser Val Leu Ala Ala Thr Ala Ser Ile
        35                  40                  45

Met Gly Val Val Ser Val Ala Val Gly Ser Gln Phe Pro Phe Arg Tyr
    50                  55                  60

Asn Tyr Thr Ile Thr Lys Gly Leu Asp Ile Leu Met Leu Ile Leu Asn
65                  70                  75                  80

Met Leu Glu Phe Cys Ile Ala Val Ser Ile Ser Ala Phe Gly Cys Lys
                85                  90                  95

Ala Ser Cys Cys Asn Ser Ser Glu Val Leu Val Val Leu Pro Ser Asn
            100                 105                 110

Pro Ala Val Thr Val Met Ala Pro Pro Thr Pro Leu Asn Glu Gly Leu
        115                 120                 125

Arg Pro Pro Lys Asp Gln Gln Thr Asn Ala Pro Glu Ile Tyr Ala Asp
    130                 135                 140

Cys Asp Thr Arg Ser Leu Thr
145                 150
```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 365 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

CTATGGGGAC CAAAGTGNTT TTTCNTTCAG GAAGTGGAGA TGCATGGCCA TCTCCCCCTC 60

CCTTTTTCCT TCTCNTGNTT TTCTTTCCCC ATAGAAAGTA CCTTGAAGTA GCACAGTCCG 120

TCCTTGCATG TGCNCGNGCT NTCNTTTGAG TAAAAGTATA CATGGAGTAA AAATCATATT 180

AAGCATCAGA TTCAACTTAT ATTTTNTATT TCATNTTCTT CCTTTCCCTT CTCCCACNTT 240

NTACTGGGCA TAATTATATN TTAATCATAT ATGGAAATGT GCAACATATG GTATTTGTTA 300

AATACGTTTG TTTTTATTGC AGAGCAAAAA TAAATCAAAT TAGAAGCAAA AAAAAAAAAA 360

AAAAA 365

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 689 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CCCANAGAGN CCTAGGAAGA TGAACAAACG ACAGCTCTAC TACCAGGTTT TAAACTTTGC 60

CATGATCGTG TCTTCTGCGC TCATGATCTG GAAAGGCCTG ATTGTTCTCA CGGGCAGCGA 120

GAGTCCCATC GTGGWGGTAC TCAGTGGCAG TATGGAGCCG GCCTTCCACA GAGGAGATCT 180

BCTGTTCCTC ACGAATTTCC GGGAGGACCC CATCAGAGCT GGTGAAATAG TTGTTTTTAA 240

GGTTGAAGGA AGAGACATTC CGATAGTTCA CAGAGTAATC AAGGTTCATG AAAAAGATAA 300

TGGTGACATC AARTTTCTGA CTAAAGGAGA TAATAATGAA GTYGATGATA GAGGCTTGTA 360

CAAAGAAGGC CAGAACTGGC TGGAAAAGAA GGACGTGGTG GGAAGAGCAA GANGGTTTTT 420

ACCATATGTT GGTATGGTCA CCATAATAAT GAATGACTAT CCAAAATTCA AKTATGCTCT 480

TTTGGCTGTA ATGGGTGCAT ATGTGTTACT AAAACGTGAA TCCTAAAATG AGAAGCAGTT 540

CCTGGGACCA GATTGAAATG AATTCTGTTG AAAAAGAGAA AAACTAATAT ATTTGAGATG 600

TTCCATTTTC TGTATAAAAG GGAACAGTGT GGAGATGTTT TTGTCTTGTC CAAATAAAAG 660

ATTCACCAGT AAAAAAAAAA AAAAAAAAA 689

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 168 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
Met Asn Lys Arg Gln Leu Tyr Tyr Gln Val Leu Asn Phe Ala Met Ile
1               5                  10                  15

Val Ser Ser Ala Leu Met Ile Trp Lys Gly Leu Ile Val Leu Thr Gly
            20                  25                  30

Ser Glu Ser Pro Ile Val Xaa Val Leu Ser Gly Ser Met Glu Pro Ala
        35                  40                  45

Phe His Arg Gly Asp Leu Leu Phe Leu Thr Asn Phe Arg Glu Asp Pro
    50                  55                  60

Ile Arg Ala Gly Glu Ile Val Val Phe Lys Val Glu Gly Arg Asp Ile
65                  70                  75                  80

Pro Ile Val His Arg Val Ile Lys Val His Glu Lys Asp Asn Gly Asp
                85                  90                  95

Ile Lys Phe Leu Thr Lys Gly Asp Asn Asn Glu Val Asp Asp Arg Gly
            100                 105                 110

Leu Tyr Lys Glu Gly Gln Asn Trp Leu Glu Lys Lys Asp Val Val Gly
        115                 120                 125

Arg Ala Arg Xaa Phe Leu Pro Tyr Val Gly Met Val Thr Ile Ile Met
    130                 135                 140

Asn Asp Tyr Pro Lys Phe Xaa Tyr Ala Leu Leu Ala Val Met Gly Ala
145                 150                 155                 160

Tyr Val Leu Leu Lys Arg Glu Ser
                165
```

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 309 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CTCTCCCCCC CCCCTCTCTC TCTCTCTCGC ATACTAACTA GGTTTGACTG TATTACTCGT 60

ACCAGATTTA AAATTAGACT AGCCTTGCCA CAACGCCCTA CTGAGAGGTA CTGTCGAACT 120

GTAGACAGCA TGATGTTCTT TGATGGTGAA AGTCTAAATC TGGACCGTGT TCAGAGATAC 180

CAAATGATGA GGCTGAAAAG GGGAAAGGGG GTTCTTCAGT CTCTTCTTCT TCTTCTTTTT 240

ATTTTTTTTT CCATGATGTT TTCTCTATGG CCAGTGCAAA TGGTGTTGTC ACCCTTGCAT 300

GTTGCCAAC 309

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Met Met Phe Phe Asp Gly Glu Ser Leu Asn Leu Asp Arg Val Gln Arg
1 5 10 15

Tyr Gln Met Met Arg Leu Lys Arg Gly Lys Gly Val Leu Gln Ser Leu
20 25 30

Leu Leu Leu Leu Phe Ile Phe Phe Ser Met Met Phe Ser Leu Trp Pro
35 40 45

Val Gln Met Val Leu Ser Pro Leu His Val Ala Asn
50 55 60

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 257 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

AGGTCTCTCT GGTTCTTTCT ATATCATCAT TTTATTATTA TGTCCTAATA TAAAGTACTG 60

GCTCATAGGG CCAGGGTATT ATTATAGAAT ATTATTNTCG CATGTAAACA AAGATATCTT 120

TGCTTTAAGA TGTGAGAAGA AATGAATTTA CTTTGTTTGC ATTAAGTTAN GGAAGAGTTG 180

TAATATATAC TTTAAGAAAG AAGAGAAGAA AACTAGTATC TNTAAGCGGT AAAAAAAAAA 240

AAAAAAAAAA AAAAAAA 257

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 467 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CACGAGGATT GATTTCCATC TTGCCTCTCC ANAAGGCAAA ACCTTAGTTT TTGAACAAAG 60

AAAATCAGAT GGAGTTCACA CTGNTANANA CTGAANTTGG TGATTACATG TTCTGCTTTG 120

ACAATACATT CAGCACCATT TCTGAGAANG TGATTTTCTT TGAATTAATC CTGGATAATA 180

TGGGAGAACA GGCACAAGAA CAAGAAGATT GGAAGAAATA TATTACTGGC ACAGATATAT 240

TGGATNTNAN NCTGGAAGAC ATCCTGGAAT CCATCAACAG CATCAAGTCC AGACTAAGCA 300

AAAGTGGGCA CATACAAACT CTGCTTAGAG CATTTGAAGC TCGTGATCGA AACATACAAG 360

AAAGCAACTT TGATAGAGTC AATTTCTGGT CTATGGTTAA TTTAGTGGTC ATGGTGGTGG 420

TGTCAGCCAT TCAAGTTTAT ATGCTGAAGA GTCTGTTTGA AGATAAG 467

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 133 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Met Glu Phe Thr Leu Xaa Xaa Thr Glu Xaa Gly Asp Tyr Met Phe Cys
1 5 10 15

Phe Asp Asn Thr Phe Ser Thr Ile Ser Glu Xaa Val Ile Phe Phe Glu
20 25 30

Leu Ile Leu Asp Asn Met Gly Glu Gln Ala Gln Glu Gln Glu Asp Trp
35 40 45

Lys Lys Tyr Ile Thr Gly Thr Asp Ile Leu Asp Xaa Xaa Leu Glu Asp
50 55 60

Ile Leu Glu Ser Ile Asn Ser Ile Lys Ser Arg Leu Ser Lys Ser Gly
65 70 75 80

His Ile Gln Thr Leu Leu Arg Ala Phe Glu Ala Arg Asp Arg Asn Ile
85 90 95

Gln Glu Ser Asn Phe Asp Arg Val Asn Phe Trp Ser Met Val Asn Leu
100 105 110

Val Val Met Val Val Val Ser Ala Ile Gln Val Tyr Met Leu Lys Ser
115 120 125

Leu Phe Glu Asp Lys
130

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 387 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

TGTTTGAAGA TAAGAGGAAA AGTAGAACTT AAAACTCCAA ACTAGAGNAC GTAACATTGA 60

AAAATGAGGC ATAAAAATGC AATAAACTGT TACAGTCAAG ACCATTAATG GTNTTNTCCA 120

AAATATTTTG AGATATAAAA GTAGGAAACA GGTATAATTT TAATGTGAAA ATTAAGTNTT 180

CACTTTCTGT GCAAGTAATC CTGCTGATCC AGTTGTACTT AAGTGTGTAA CAGGAATATT 240

TTGCAGAATA TAGGTTTAAC TGAATGAAGC CATATTAATA ACTGCATTTT CCTAACTTTG 300

AAAAATTTTG CAAATGTCTT AGGTGATTTA AATAAATGAG TATTGGGCCT AATTGCAAAA 360

AAAAAAAAAA AAAAAAAAAA AAAAAAA 387

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 279 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GAATTCTCTT GAAGNTGGGG GGTGCNGGNN GGGGAAANCG NNTCTCCNNT CCANAAGCGG 60

GGGCCNTTTT GTCCGTNNNC TTGTGNAAAA AANCCCGGNG NTGGTGAACG CTGNTNTTAN 120

TTACTCCAAA CCTCGANTGG NCNNTTNGTG GTNCNNCGCC GAGGNTGANN TGGNTCCCCC 180

CCCCCCTGNT NNAATNCCNA AAACTNTTCN GAACCCGAAA ANAATTNTCC ATTCTGCCNN 240

NANTGGTTTC NTCCNNCNNC TCCTNATTAA AGAAGCNNT 279

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 337 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

GGCGGGTGAC ATTCAGCCGG CGGTTCGGGG GGACGGANTC TCCATTCCAG AACCATGGCC 60

CAATTTGTCC GTAACCTTGT GGAGAAGACC CCGGCGCTGG TGAACGCTGC TGTGACTTAC 120

TCGAAGCCTC GATTGGCCAC ATTTTGGTAC TACGCCAAGG TTGAGCTGGT TCCTCCCACC 180

CCTGCTGAGA TCCCTAGAGC TATTCAGAGC CTGAAAAAAA TAGTCAATAG TGCTCAGACT 240

GGTAGCTTCA AACAGCTCAC AGTTAAGGAA GCTGTGCTGA ATGGTTTGGT GGCCACTGAG 300

GTGTTGATGT GGTTTTATGT CGGAGAGATT ATAGGCA 337

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 94 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Met Ala Gln Phe Val Arg Asn Leu Val Glu Lys Thr Pro Ala Leu Val
1 5 10 15

Asn Ala Ala Val Thr Tyr Ser Lys Pro Arg Leu Ala Thr Phe Trp Tyr
20 25 30

Tyr Ala Lys Val Glu Leu Val Pro Pro Thr Pro Ala Glu Ile Pro Arg
35 40 45

Ala Ile Gln Ser Leu Lys Lys Ile Val Asn Ser Ala Gln Thr Gly Ser
50 55 60

Phe Lys Gln Leu Thr Val Lys Glu Ala Val Leu Asn Gly Leu Val Ala
65 70 75 80

Thr Glu Val Leu Met Trp Phe Tyr Val Gly Glu Ile Ile Gly
85 90

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 345 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

AAATTANAGG AAGANCCTNT TGAAAAAATT TNTGTTTGTN AAAAAGNTAG GGNAATTGTT 60

ATTTTGGAAA TAGCCTNCCC NAGNGNGGAN AGGGGGGNAT TTTAAGNANG NTTTTTTGNA 120

AAATTTTTNG NCGNNGGNNA GAANCNAAAA AGNGGAATTT GNNTTTTAAG GGGGNTANTT 180

GNTTGTTTGG GTTTAANACC CTTGCCAAAA NNAAANACCC CCAAGNNANT TNAANNAGGG 240

TATAANTTAG NATTTTTCCC TGGANTTAAA NAGNANATTA TATNCTGGAA NAAANGNAAN 300

GGTTGGTATN AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAA 345

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 456 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

AGAGATTCAG GACCTGCAGA GTCGCCAGAA GCATGAAATT GAATCTTTGT ATACTAAACT 60

GGGCAAGGTT CCCCCTGCTG TCATTATTCC CCCAGCTGCT CCTCTGTCGG GGAGAAGAAG 120

GAGACCCACT AAAAGCAAAG GCAGCAAGTC TAGTCGCAGC AGCTCATTGG GCAATAAAAG 180

CCCACAGCTT TCAGGCAACC TGTCTGGTCA GAGTGGAACT TCAGTCTTAC ACCCCCAACA 240

GACCCTCCAC CCTCCTGGCA ACATCCCANA NTCCGGGCAG AATCAGCTGT TACAGCCCCT 300

TAAGCCATCT CCCTCCAGTG ACAACCTCTA TTCAGCCTTC ACCAGTGATG GTGCCATTTC 360

AGTACCAAGC CTTTCTGCTC CAGGTCAAGG AACCAGCAGC ACAAACACTG TTGGGGCAAC 420

AGTGAACAGC CAAGCCGCCC AAGCTCAGCC TCCTGC 456

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 130 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Met Lys Leu Asn Leu Cys Ile Leu Asn Trp Ala Arg Phe Pro Leu Leu
1 5 10 15

Ser Leu Phe Pro Gln Leu Leu Leu Cys Arg Gly Glu Glu Gly Asp Pro
20 25 30

Leu Lys Ala Lys Ala Ala Ser Leu Val Ala Ala Ala His Trp Ala Ile
35 40 45

Lys Ala His Ser Phe Gln Ala Thr Cys Leu Val Arg Val Glu Leu Gln
50 55 60

Ser Tyr Thr Pro Asn Arg Pro Ser Thr Leu Leu Ala Thr Ser Xaa Xaa
65 70 75 80

Pro Gly Arg Ile Ser Cys Tyr Ser Pro Leu Ser His Leu Pro Pro Val
85 90 95

Thr Thr Ser Ile Gln Pro Ser Pro Val Met Val Pro Phe Gln Tyr Gln
100 105 110

Ala Phe Leu Leu Gln Val Lys Glu Pro Ala Ala Gln Thr Leu Leu Gly
115 120 125

Gln Gln
130

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 188 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

TACCCTGCCC TCCTCCCTTT TTTNNACCCC TCTCTTTTTT ATTTTTTCTT TGCTCTTTAG 60

AACCCAGTGA AAAATACCAG GGTACTGGGG TGCAACTCTT TCTTATGATA GGTCATTAGT 120

GCTTTAAGCA AAAGATATTA GCAGCTTTGA CTGCAGCATT AGCAATTAGG NAAAAAAAAA 180

AAAAAAAA 188

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 752 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CCTTATGGCC TACTTTAAAA AAAAACCAAT ACCAAAGAAG CCTACAATGT TGGCCTTAGC 60

CAAAATTCTG TTGATTTCAA CGTTGTTTTA TTCACTTCTA TCGGGGAGCC ATGGAAAAGA 120

AAATCAAGAC ATAAACACAA CACAGAACAT NGCAGAAGTT TTTAAAACAA TGGAAAATAA 180

ACCTATTTCT TTGGAAAGTG AAGCAAACTT AAACTCAGAT AAAGAAAATA TAACCACCTC 240

AAATCTCAAG GCGAGTCATT CCCCTCCTTT GAATCTACCC AACAACAGCC ACGGAATAAC 300

AGATTTCTCC AGTAACTCAT CAGCAGAGCA TTCTTTGGGC AGTCTAAAAC CCACATCTAC 360

CATTTCCACA AGCCCTCCCT TGATCCATAG CTTTGTTTCT AAAGTGCCTT GGAATGCACC 420

TATAGCAGAT GAAGATCTTT TGCCCATCTC AGCACATCCC AATGSTACAC CTGCTCTGTY 480

TTCARAAAAC TTCACTTGGT CTTTGTCAAT GACACCGTGA AAACTCCTGA TAACAGTTCC 540

ATTACAGTTA GCATCCTCTY TTCARAACCA ACTTCTCCAT CTGTGACCCC CTTGATAGTG 600

GAACCAAGTG GATGGNTTAC CACAAACAGT GATAGNTTCA CTGGGTTTAC CCCTTATCAA 660

GNAAAAACAA CTTTACAGCC TACCTTAAAA TTCACCAATA ATTCAAAACT NTTTCCAAAT 720

ANGTCAGATC CCCCAAAAAA AAAAAAAAAA AA 752

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 157 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Met Leu Ala Leu Ala Lys Ile Leu Leu Ile Ser Thr Leu Phe Tyr Ser
1 5 10 15

Leu Leu Ser Gly Ser His Gly Lys Glu Asn Gln Asp Ile Asn Thr Thr
20 25 30

Gln Asn Xaa Ala Glu Val Phe Lys Thr Met Glu Asn Lys Pro Ile Ser

35 40 45

Leu Glu Ser Glu Ala Asn Leu Asn Ser Asp Lys Glu Asn Ile Thr Thr
50 55 60

Ser Asn Leu Lys Ala Ser His Ser Pro Pro Leu Asn Leu Pro Asn Asn
65 70 75 80

Ser His Gly Ile Thr Asp Phe Ser Ser Asn Ser Ser Ala Glu His Ser
85 90 95

Leu Gly Ser Leu Lys Pro Thr Ser Thr Ile Ser Thr Ser Pro Pro Leu
100 105 110

Ile His Ser Phe Val Ser Lys Val Pro Trp Asn Ala Pro Ile Ala Asp
115 120 125

Glu Asp Leu Leu Pro Ile Ser Ala His Pro Asn Xaa Thr Pro Ala Leu
130 135 140

Xaa Ser Xaa Asn Phe Thr Trp Ser Leu Ser Met Thr Pro
145 150 155

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 417 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

AAGCTTGGCA CGAGGTCTTT AGAAGAACTA CAAAACCTGA ATGGAAAACT TCGAAGTGAA 60

GGACAAGGNA ATATGGGCTT TACTAGGCAG AATCACAGGG CAGAAGTTGA ATATACCGGC 120

AATTTTGAGA GCACCCAAGG AGAGAAAACC AAGTAAAAAA AGAAGGAGGC ACACAAAAGA 180

CATCTACTCT TCCTGCAGTA CTTTATAGTT GTGGGATTTG TAAGAAGAAC CATGATCAGC 240

ATCTTCTTTT ATTGTGTGAT ACCTGTAAAC TACATTACCA TTTTGGATGT CTGGATCCTC 300

CTCTAACAAG GATGCCAAGA AAGACCCAAA ACAGTTATTG GCAGTGCTCG GAATGTGACC 360

AGGCAGGGAG CAGTGACATG GAAGCAGATA TGGCCATGGA AACCCTACCA GATGGAA 417

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 35 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Met Pro Arg Lys Thr Gln Asn Ser Tyr Trp Gln Cys Ser Glu Cys Asp
1 5 10 15

Gln Ala Gly Ser Ser Asp Met Glu Ala Asp Met Ala Met Glu Thr Leu
20 25 30

Pro Asp Gly
35

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 359 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

TCTGTGTTCA GTATAATTTT ATTTTTCTCA ACCTTAAATA TGAACTTAGG AAATAAGGAG 60

GGAAGTACAA AGATTATTGA CTATACAACN TACCAGCTGA AAGAAAGATC TTCATCAACA 120

TCTGTATCTT TCCAGAGGTA TACAGAATTA AAATTNNATN TTCAAGCTTT AATGATCCAG 180

TTTTAAGTCA ACGGCAGAAG TATGTTGAAT ATTTCATCAC TCAATCTTGA ACTGATTTAG 240

AAGAGACTCT TTGCTGAAAT TGAATTGCAC TTATACATGT AAATTGTCAA CATGTAATTT 300

GGAATTTTCT GATTAATAAA TGTGGTTTTG GACATCTAAA AAAAAAAAAA AAAAAAAAA 359

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 675 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

CTCNCAAATC GGCNCGNGCA ACGAACGGCT TGGGCGCGGA CTGGTATCCG GGGACTGTGA 60

CTTGCAGGGT CCGCCATGGA GCCAGAGCAG ATGCTGGAGG GACAAACGCA GGTTGCAGAA 120

AATCCTCACT CTGAGTACGG TCTCACAGAC AACGTTGAGA GAATAGTAGA AAATGAGAAG 180

ATTAATGCAG AAAAGTCATC AAAGCAGAAG GTAGATCTCC AGTCTTTGCC AACTCGTGCC 240

TACCTGGATC AGACACTTGT GCCTATCTTA TTACAGGGAC TTGCTGTGCT TGCCAAGGAA 300

AGACCACCAC ATCCCATTGA ATTTCTAGCA TCTTATCTTT TAAAAAACAA GGCACAGTTT 360

GAAGATYGAA ACTGAMTTAA TGGGRAGAAC AGAAAAATTT AGTTGSTACT GTAGATTTAC 420

ATGATTAAGA RGCAGCTTTA ATTGCCATGA TCATTCCCTT TTTTTGGAAG GATAAGNACC 480

TTNCGGANAA CAGNACCTAT TTTTGGGATT GCAGNAGNTA AAATATTTCC CNTATTTTGA 540

NTTAATNACC ATAAACCNTA CCTATTTAAT GNGNGTATTT TGTGCAATTT TTTTTTNAGN 600

TTGTTTTTAA ATTTGTTTTT AAAATGACCT TNAAAATNAA NTGTNNAAAC ACCNTTTAAA 660

AAAAAAAAAA AAAAA 675

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 99 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Met Glu Pro Glu Gln Met Leu Glu Gly Gln Thr Gln Val Ala Glu Asn
1 5 10 15

Pro His Ser Glu Tyr Gly Leu Thr Asp Asn Val Glu Arg Ile Val Glu
20 25 30

Asn Glu Lys Ile Asn Ala Glu Lys Ser Ser Lys Gln Lys Val Asp Leu
35 40 45

Gln Ser Leu Pro Thr Arg Ala Tyr Leu Asp Gln Thr Leu Val Pro Ile
50 55 60

Leu Leu Gln Gly Leu Ala Val Leu Ala Lys Glu Arg Pro Pro His Pro
65 70 75 80

Ile Glu Phe Leu Ala Ser Tyr Leu Leu Lys Asn Lys Ala Gln Phe Glu
85 90 95

Asp Xaa Asn

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 552 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

CACGAGGGTT TGGTGAGGAA ATTACCAGAG AACTATTAAA GACTTGGATG CTCTTCTCGG 60

CTTTGCTATT AAGTAAGTTG GACAAGTTGT TTGGCTTCTT TGAGCCTCTG TTTTCTCCAT 120

TCTAAAATTC TAAAATGGGA GTGTTGAATT AGATCAGTGG CTTTCGAACT TTCTGCTCCT 180

AGTAGTGAGA AATACATTTT ACTCCACTCC CTGGTATGTA CACGCATTCC TGTGTTTTGT 240

GAAAACCTGA CACCATGCTC CTCCCTCACT ACATGTAAAA CACTTTTATT CATTAAAAAG 300

AAAACTGACT GGCTTGGACC TACAAATTAG TTTCATTATT TGTTAATGTT TGAAAGCCAT 360

TAAAAGATGA ATATTAAGGT TTCTTTATAC TCAATACTTG TAGTTTTGTT TGGGGGAATG 420

AGAGGATGCC CTTGGTACCT TTGTGAGGCC TCTCCACTGA GGGTCAATCA TGACTTCTGT 480

TTTAAACCAG CCCATCCCAT CTTCTCCAGC TGCTCTCCTT ATGTCTTGCT TCTCTCCCCT 540

CCAACCTTCT CA 552

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 62 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Met Asn Ile Lys Val Ser Leu Tyr Ser Ile Leu Val Val Leu Phe Gly
1 5 10 15

Gly Met Arg Gly Cys Pro Trp Tyr Leu Cys Glu Ala Ser Pro Leu Arg
20 25 30

Val Asn His Asp Phe Cys Phe Lys Pro Ala His Pro Ile Phe Ser Ser
35 40 45

Cys Ser Pro Tyr Val Leu Leu Leu Ser Pro Pro Thr Phe Ser
50 55 60

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 318 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CAGGGCCCCA TCCTTCAGTG CATTGCACAC TTTGCATGNT GGGTCAGGGA AGATTGTGGA 60

GAGAGGACAG TGCACATGGT TTCCCCCACN TNGNCTGCGT GGGGGTATGT CCTGCTTCCG 120

CCACTTCCAA CTGTGGCANT TGGGCACGCC CCTNTCAGGG CACCTTCCCT TTTTGTTTCC 180

GCAAAATGAG GTTGTAATAG TGCCTGCCGC ACTGTNTGGC ACACAGTAAG NTCTCAAGAA 240

ATGTTAGCTG TTGTTGCCGT TAGAACACCA TAGNTAGAAT ACCATACNTG GCATTCACTT 300

AAAAAAAAAA AAAAAAAA 318

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 310 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

ATTGAGGAAA ACCACAAAAA ACTTCAAAAC AGCTACAACG GGAAAAAGAG AGTTTTGTCC 60

CACAGTCAGC AGGCCACTAG TTTATTAACT TCCAGTCACC TTGATTTTTG CTAAAATGAA 120

GACTCTGCAG TCTACACTTC TCCTGTTACT GCTTGTGCCT CTGATAAAGC CAGCACCACC 180

AACCCAGCAG GACTCACGCA TTATCTATGA TTATGGAACA GATAATTTTG AAGAATCCAT 240

ATTTAGCCAA GATTATGAGG ATAAATACCT GGATGGAAAA AATATTAAGG AAAAAGAAAC 300

TGTGATAATA 310

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 65 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Met Lys Thr Leu Gln Ser Thr Leu Leu Leu Leu Leu Leu Val Pro Leu
1 5 10 15

Ile Lys Pro Ala Pro Pro Thr Gln Gln Asp Ser Arg Ile Ile Tyr Asp
20 25 30

Tyr Gly Thr Asp Asn Phe Glu Glu Ser Ile Phe Ser Gln Asp Tyr Glu
35 40 45

Asp Lys Tyr Leu Asp Gly Lys Asn Ile Lys Glu Lys Glu Thr Val Ile
50 55 60

Ile
65

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 303 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

CCCAAGNAAN TTTCAANTTT TTGCCTTTNC TGGCCTTTAN TGGATCCCNA AAGCATTTAA 60

GGNANATGTT CCNAAAANTT TGNAAAGNTA AANGTTTCCC ATGATCGCTC ATTTTTTTTT 120

TATGATTCAN ANGTTATTCC TTATAAAGTA AGNANTTTGT TTTCCTCCTA TCAAGGCAGN 180

TATTTTATTA AATTTTTCAN TTAGTTTGAG NAATAGCAGA TAGTTTCATA TTTAGGGAAA 240

NTTTCCAAAT AAAATAAATG TTATTNTTTG ATAAAGAGNT AAAAAAAAAA AAAAAAAAAA 300

AAA 303

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 418 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

AAGCTTGNGC ACGNGGCACA AGTAGCTACG NCTGCAAGCA CCTGCCACCA TAAAGGGGNT 60

GCATTTTGCC ACCATAAANG GGNTGCATTT TTTTAAAAAG CCTAGGCNGC TCTAACATCA 120

TCTGATATGG ACACAANGCN AACAGTTTCC NTATNTACAT CCNTACCTCT AAAAGATACT 180

TCAAAGTGAC AAAAACGTGT TCCTTCCCCA CTTAGAGACA ATGATTAACA GGGCCCTATA 240

TGTTCTTACC ACATACAGAG GATGCATTTA TTTTTGCTCT ATGACACTTG CAAAAATCTC 300

TACTGTAATT AATTTGGGTC TATTATTAAC TCTCTGTTCC ATCATAGAAT GTGGCCAGGC 360

CTTACAATGG AGAGCCAGAG TTAAAACTTC AAGTTGCATC TGTTTTTGGG CTGAGTCA 418

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Met Thr Leu Ala Lys Ile Ser Thr Val Ile Asn Leu Gly Leu Leu Leu
1 5 10 15

Thr Leu Cys Ser Ile Ile Glu Cys Gly Gln Ala Leu Gln Trp Arg Ala
20 25 30

Arg Val Lys Thr Ser Ser Cys Ile Cys Phe Trp Ala Glu Ser
35 40 45

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 331 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

AGTTTGTTCT GTAAATATTT NGAAAAGTGA CAGCTNTCAA CTTCAGGGTA ACTATTTCTA 60

AAAATGTAAA TANGTATTAA TCCTTGTATC TTTTATGGTA ATTTNGCATA TTGATATGAA 120

TTANATAAAA TTGTTTAAAA TAAAAGGTGT CCTTGAATTA CTGACCACCC ATAGATGTNT 180

ACTGTTACCA GGTTTTACAA TGCAAATTTT CACTAATACC TGGGTTTAAT ACAGCTCACA 240

TCACTGAATG TTACACATGA GTTTAAATGG GTTAATATAC AGGTTTTGTT ATAATAAAGT 300

TACTGATTAA ATTAAAAAAA AAAAAAAAAA A 331

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 583 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

CACGNGGGTG AGGCCGACTG CTGAAGACAG CTCGCCACCC TCCTTGCCTC CACTCCAATC 60

CAGGGGCTGG GGCCACATTC TTTGCCTTCA TTTATCCTCA GATCAGGTGA GATCGACAGG 120

AGGTGTTGAT GGCAGTGCCA GCAATTATTG CTAATCCGTT TGCATCCTTA TGCATAGATC 180

TGAATTCAGA CTTTGTGAAT TTCCAGAGGT GTGGGTNATA TAATAGAATT CAGTGAGTGG 240

GCATGGCTGA TCTTGTGCAA ATTAAAAGTT ATGGGGCATA AGAATAGCAA AAGTTGAACT 300

TCTTTTAAAA AGGAAAGTAC CCTGAGAGCC AGTATTGGTT GAGGCTCTTC AGTATGCCCA 360

GGTTGGCAGC ACTGAGAACC GCAGGAACGG CCTGTTGTTA CAAAAAGGAG ATTGACTCAG 420

CTGCCCTTGG TGCATCTGAC TGACTATGAC TGCTGAGAGA TTCCAAGGAC CCTTAATGCC 480

AGGGCTAACC TCTCCATGTG CAGTGAGACC TCTGGAGGAA GTGTCATCCT CTGGCTTTGT 540

GTGGTACTCA TTATGGTGCA GTGCGGGCAT GAAATGAAGA CAC 583

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Met Cys Ser Glu Thr Ser Gly Gly Ser Val Ile Leu Trp Leu Cys Val
1 5 10 15

Val Leu Ile Met Val Gln Cys Gly His Glu Met Lys Thr
20 25

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 311 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

CCCAAATAGG CTTACAGATA CGATATGTTT TAAATGTTTN GTATTTAACA AAAACATACT 60

GACACTGTTT GGAAATGGCA ACAGGAAGAT AGCAAAATGA ATACTAACAT TACGAAAAGA 120

TGAACAGGTA CATGTTCCAA GGCAGGTGGC TGTGAACTTC CTCTGAGTGA AGGCATCCCC 180

TCCAGCACCT TTCAGCCTGC TAGTTAGGAC GACCCGCCGC CACCCTCCAG GACNTCCAGC 240

CCTGCANTGC NTTTCTTTTN TTTTAAATAA TTCTTCATTG AGTTCTAATA TGTAAAAAAA 300

AAAAAAAAAA A 311

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 405 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

AAGCTTGGCA CGAGGGCGGT TGAGGCCTTC GGTGGTGAAC GAGTCTCCAG CACCATGTCT 60

GGTTTGTCTG GCCCACCAGC CCGGCGCGGC CCTTTTCCGT TAGCGTTGCT GCTTTTGTTC 120

CTGCTCGGCC CCAGATTGGT CCTTGCCATC TCCTTCCATC TGCCCATTAA CTCTCGCAAG 180

TGCCTCCGTG AGGAGATTCA CAAGGACCTG CTAGTGACTG GCGCGTACGA GATCTCCGAC 240

CAGTCTGGGG GCGCTGGCGG CCTGCGCAGC CACCTCRAGA TCACAGATTC TGCTGGCCAT 300

ATTCTCTACT CCAAAGAGGA TGCAACCAAG GGGAAATTTG CCTTTACCAC TGAAGATTAT 360

GACATGTTTG AAGTGTGTTT TGAGAGCAAG GGAACAGGGC GGATA 405

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 117 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

```
Met Ser Gly Leu Ser Gly Pro Pro Ala Arg Arg Gly Pro Phe Pro Leu
1               5                  10                  15

Ala Leu Leu Leu Leu Phe Leu Leu Gly Pro Arg Leu Val Leu Ala Ile
            20                  25                  30

Ser Phe His Leu Pro Ile Asn Ser Arg Lys Cys Leu Arg Glu Glu Ile
        35                  40                  45

His Lys Asp Leu Leu Val Thr Gly Ala Tyr Glu Ile Ser Asp Gln Ser
    50                  55                  60

Gly Gly Ala Gly Gly Leu Arg Ser His Leu Xaa Ile Thr Asp Ser Ala
65                  70                  75                  80

Gly His Ile Leu Tyr Ser Lys Glu Asp Ala Thr Lys Gly Lys Phe Ala
                85                  90                  95

Phe Thr Thr Glu Asp Tyr Asp Met Phe Glu Val Cys Phe Glu Ser Lys
            100                 105                 110

Gly Thr Gly Arg Ile
        115
```

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 225 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

```
TCTTTCAATT TACCTTGTGA AAACACCCTT AACTTTTTCT TNACCCTTAG CTGAAATGTT     60

NACATAGCTT NTGGTGATAT CTTTTCATGA TTTTATATNT CTTAAAATGG TGATGGATGT    120

GACACCTCAT AAAAGTGAGC TTTGAACTGT AGATAACTCT TAAAGAAAAT GTCATTTTAG    180

ACAATTAAAA TATTTGTGCT CAAAAAAAAA AAAAAAAAAA AAAAA                    225
```

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 525 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

CGAGGGCAGG TCAGTCAGGT TCCTGGGCGC TCTGTTACAC AAGCAAGATA CAGCCAGCCC 60

CACCTAATTT TGTTTCCCTG GCACCCTCCT GCTCAGTGCG ACATTGTCAC ACTTAACCCA 120

TCTGTTTTCT CTAATGCACG ACAGATTCCT TTCAGACAGG ACAACTGTGA TATTTCAGTT 180

CCTGATTGTA AATACCTCCT AAGCCTGAAG CTTCTGTTAC TAGCCATTGT GAGCTTCAGT 240

TTCTTCATCT GCAAAATGGG CATAATACAA TCTATTCTTG CCACATCAAG GGATTGTTAT 300

TCCTTTAAAA AAAAACCAAT ACCAAAGAAG CCTACAATGT TGGCCTTAGC CAAAATTCTG 360

TTGATTTCAA CGTTGTTTTA TTCACTTCTA TCGGGGAGCC ATGGAAAAGA AAATCAAGAC 420

ATACACACAA CACAGAACAT TGCAGAAGTT TTTAANACAA TGGAAAATAA ACCTATTTCT 480

TTGGAAAGTG AAGCAAACTT AAACTCAGAT AAAGNAAATA TAACC 525

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 63 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Met Leu Ala Leu Ala Lys Ile Leu Leu Ile Ser Thr Leu Phe Tyr Ser
1 5 10 15

Leu Leu Ser Gly Ser His Gly Lys Glu Asn Gln Asp Ile His Thr Thr
20 25 30

Gln Asn Ile Ala Glu Val Phe Xaa Thr Met Glu Asn Lys Pro Ile Ser
35 40 45

Leu Glu Ser Glu Ala Asn Leu Asn Ser Asp Lys Xaa Asn Ile Thr
50 55 60

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 302 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

TCAAAAGGTN ACACAAAATT ACTGTCACGT GGATTTTGTC AAGGAGAATC ATAAAAGCAG 60

GAGACCAGTA GCAGAAATGT AGACAGGATG TATCATCCAA AGGTTTTCTT TCTTACAATT 120

TTTGGCCATC CTGAGGCATT TACTAAGTAG CCTTAATTTG TATTTTAGTA GTATTTTCTT 180

AGTAGAAAAT ATTTGTGGAA TCAGATAAAA CTAAAAGATT TCACCATTAC AGCCCTGCCT 240

CATAACTAAA TAATAAAAAT TATTCCACCA AAAAATTNTA AAACAAAGNA AAAAAAAAAA 300

AA 302

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 628 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

CACGAGGTTT CAGACCAGCT TGTGTCAATA GGGTCCTACA GAGCAGCTGA TATCAGCAGT 60

TTTACTAGTA TGCAGGACCT GAAAGAATAT CTCAAAGGGA AAACAATGTT TCATAATGTT 120

CAGGAAGTTA TCTATAGAGC AGCTAAGGAG CTATAATCTT GTAACAGAGT CTACGTGATT 180

GTAGGACAAT AGGCACCACA CAAATATGAG GAAGCAGGTC AGAGAGCGGG CTGACTTAAT 240

GATTAATGCT GAATGTGCTA CAAGCTTGTT TCATTTTCAT TTCTCCTCCT CCCTTTTTTC 300

CTGATTAATT TAATAAAGTT CATAGGGGAG GCTTCAAACA CATGAGAAAT TAAAACCTTT 360

ATTACCAGAG TCAGAGCCTG ACTATATTGA TTGAGTGAAG CTTTCCTTTA TAAAATGCAA 420

AGCATGTAAA CAATTCCAAC ACAGTAACAT ATTCATGAGT TTTTAAATTC ATGAGTTTTA 480

GAGAAAATAT TTTACTTAAA ACCAGCACTT GATGATCTCT GACAATGTTA TGTAGCCTGA 540

ACCTGGAGTT TTGGCTGATG GGTTGTCTCA GCCTGTGACA GGTTTTAGCT GGCTTTGGTT 600

CATCTTGTAT CACACCCCCA CACTCACA 628

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

Pro Glu Pro Gly Val Leu Ala Asp Gly Leu Ser Gln Pro Val Thr Gly
1 5 10 15

Phe Ser Trp Leu Trp Phe Ile Leu Tyr His Thr Pro Thr Leu Thr
20 25 30

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 436 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

AGCAGCTAAG GGGAAATAAT CTTGTAACAG GGTCTGGGTG ATTNTGAGGT AATAGGCCCC 60

AAACAACCAT GGGGAAGCAG GTCAGAGGGC AAGCTGGCNT AGTGTTTAAC ATTGAATGGG 120

CTGAAAGTTT GGTTNATTTT TGTTTCTTGT TTCTCCCCCT CCCTTCTNAC CTGAATAATT 180

TTATGAAGTT TATAGGGATG GTTTCAGGAC CTCCATTCTA TCTGTTCCTG AAATATTACA 240

AAAAGATTAT TATTGTAGCA CTNATNTAAT TGGGGTTTTA TTTCGTTGTT NGCATGTCTG 300

TTTCTTCCCC AGTGAGTTGT AAATTGCTTA AGGGCAAACA GACGCATCCT ATTTATCTGT 360

CTGTCACTAA CATTAAGCAC AGCATTTGGT ATACAGTCAT CACTCTAATA AAGTTTGAAA 420

436

AAAAAAAAAA AAAAAA

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 636 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CACGAGGGAA AAAAAGAGTT TTTTTTTTAG ATCATCAGCT ATTGTTAGTG TTTGTGTATG 60

TTATGTGTGG CTCAAGACAA CTTTGCTTCT TTTAATATAG GCAGGGAAGT CAAAAGATTG 120

GATATCCCTG CTTTATACCA AGAAAGACAA CACCCCACAT TTGCAGTGCC TGAAAACACT 180

ACCAGCCATC TGAAAAACAT GTGACTTCTA ACTTCTGTTC TTTTTTGTAG CAGTGGAATC 240

CCACGGTGAT ATCTGAGGGA TGTGGTTACC TTTTGGAGGA GGTTGACGGT TTCTAAGGAT 300

GATTCTTTCT GAGTGAAATA TTGTCAGTGT CATTGACCTT TTCATTATTT CAACTATTAT 360

TATTCCAGGT TATCAATACT CTGGCTGACC ATCATCATCG TGAGACTGAC TTTGGTGTAG 420

GAGTTCGAGA CCACCCTGGC CAACATGGCA AAACCCCATC TCCACAAAAA TTGGATAATT 480

TGATAATTAT CATTATTGGG TTTCTGAGAC GTTACACATT TAACATTNTN TTCTGCACAA 540

GTTGCCTTTG TGTGAGTATA CTAACTTTCT GTAGAGGTAN ACTTGTAATC ACAAATAAGA 600

ATAAATTATA TAAAACAAAA AAAAAAAAAA AAAAAA 636

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 105 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Phe Phe Leu Ser Glu Ile Leu Ser Val Ser Leu Thr Phe Ser Leu Phe

1 5 10 15

Gln Leu Leu Leu Phe Gln Val Ile Asn Thr Leu Ala Asp His His His
20 25 30

Arg Glu Thr Asp Phe Gly Val Gly Val Arg Asp His Pro Gly Gln His
35 40 45

Gly Lys Thr Pro Ser Pro Gln Lys Leu Asp Asn Leu Ile Ile Ile Ile
50 55 60

Ile Gly Phe Leu Arg Arg Tyr Thr Phe Asn Ile Xaa Phe Cys Thr Ser
65 70 75 80

Cys Leu Cys Val Ser Ile Leu Thr Phe Cys Arg Gly Xaa Leu Val Ile
85 90 95

Thr Asn Lys Asn Lys Leu Tyr Lys Thr
100 105

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 536 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

GGCACGAGGA GCGGGAGCTG GTGCCTTCCC GGAAGGGCTC AGAGGCGGGC TCGGGCAAGC 60

ACTTTAACCT TTTAAGCCCA ACCAGATGAG TTGCCTGCAG TTTTGGAGGC CTTCAGAGCA 120

TTTCACTAGA CCTCTGTCTG TGTCGGTCCA ATGTCTTTAG CCAAGCTTTG ATTAAAGATG 180

ACTTCCTTGT TTGCTCAAGA AATTCGCCTT TCTAAAAGAC ATGAAGAAAT AGTATCACAA 240

AGATTAATGT TACTTCAACA AATGGAGAAT AAATTGGGTG ATCAACACAC AGAAAAGGCA 300

TCTCAACTCC AAACTGTTGA GACTGCTTTT AAAAGGAACC TTAGTCTTTT AAAGGATATA 360

GAAGCAGCAG AAAAGTCACT ACAGACCAGG ATTCACCCAC TTCCACGGCC TGAGGTGGTT 420

TCTCTTGAGA CTCGTTACTG GGCATCAGTA GAAGAATATA TTCCCAAATG GGAACAGTTT 480

CTTTTAGGAA GAGCACCATA TCCTTTTGCT GTTGAAAATC AAAATGAAGC AGAAAA 536

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 119 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Met Thr Ser Leu Phe Ala Gln Glu Ile Arg Leu Ser Lys Arg His Glu
1 5 10 15

Glu Ile Val Ser Gln Arg Leu Met Leu Leu Gln Gln Met Glu Asn Lys
20 25 30

Leu Gly Asp Gln His Thr Glu Lys Ala Ser Gln Leu Gln Thr Val Glu
35 40 45

Thr Ala Phe Lys Arg Asn Leu Ser Leu Leu Lys Asp Ile Glu Ala Ala
50 55 60

Glu Lys Ser Leu Gln Thr Arg Ile His Pro Leu Pro Arg Pro Glu Val
65 70 75 80

Val Ser Leu Glu Thr Arg Tyr Trp Ala Ser Val Glu Glu Tyr Ile Pro
85 90 95

Lys Trp Glu Gln Phe Leu Leu Gly Arg Ala Pro Tyr Pro Phe Ala Val
100 105 110

Glu Asn Gln Asn Glu Ala Glu
115

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 79 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

TTTATTTAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 60

AAAAAAAAAA AAAAAAAAA 79

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What is claimed is:

1. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 28 to nucleotide 276;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AE402_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AE402_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AE402_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AE402_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

2. The composition of claim 1, further comprising a pharmaceutically acceptable carrier.

3. A method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition of claim 2.

4. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) fragments of the amino acid sequence of SEQ ID NO:2; and

(c) the amino acid sequence encoded by the cDNA insert of clone AE402_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

5. The composition of claim 4, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.

6. The composition of claim 4, further comprising a pharmaceutically acceptable carrier.

7. A method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition of claim 6.

8. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:4;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:4 from nucleotide 61 to nucleotide 513;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:4 from nucleotide 322 to nucleotide 513;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AE610_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AE610_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AE610_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AE610_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:5;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:5 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

9. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:5;

(b) fragments of the amino acid sequence of SEQ ID NO:5; and

(c) the amino acid sequence encoded by the cDNA insert of clone AE610_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

10. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 20 to nucleotide 523;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AH106_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AH106_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AH106_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AH106_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

11. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) fragments of the amino acid sequence of SEQ ID NO:8; and

(c) the amino acid sequence encoded by the cDNA insert of clone AH106_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

12. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 130 to nucleotide 309;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AH196_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AH196_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AH196_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AH196_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

13. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) fragments of the amino acid sequence of SEQ ID NO:10; and

(c) the amino acid sequence encoded by the cDNA insert of clone AH196_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

14. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:12 from nucleotide 69 to nucleotide 467;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AI6_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AI6_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AI6_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AI6_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:13;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:13 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

15. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:13;

(b) the amino acid sequence of SEQ ID NO:13 from amino acid 69 to amino acid 133;

(c) fragments of the amino acid sequence of SEQ ID NO:13; and

(d) the amino acid sequence encoded by the cDNA insert of clone AI6_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

16. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:16;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:16 from nucleotide 55 to nucleotide 337;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AJ13_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AJ13_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ13_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ13_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:17;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:17 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

17. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:17;

(b) the amino acid sequence of SEQ ID NO:17 from amino acid 12 to amino acid 94;

(c) fragments of the amino acid sequence of SEQ ID NO:17; and

(d) the amino acid sequence encoded by the cDNA insert of clone AJ13_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

18. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 33 to nucleotide 422;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 114 to nucleotide 422;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AJ27_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AJ27_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ27_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ27_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

19. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:20;

(b) fragments of the amino acid sequence of SEQ ID NO:20; and

(c) the amino acid sequence encoded by the cDNA insert of clone AJ27_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

20. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:22;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:22 from nucleotide 47 to nucleotide 517;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:22 from nucleotide 116 to nucleotide 517;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AJ142_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AJ142_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ142_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ142_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:23;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:23 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

21. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:23;

(b) fragments of the amino acid sequence of SEQ ID NO:23; and

(c) the amino acid sequence encoded by the cDNA insert of clone AJ142_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

22. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:24;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:24 from nucleotide 312 to nucleotide 417;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AK604_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AK604_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AK604_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AK604_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:25;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:25 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

23. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:25;

(b) fragments of the amino acid sequence of SEQ ID NO:25; and

(c) the amino acid sequence encoded by the cDNA insert of clone AK604_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

24. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 76 to nucleotide 372;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AK620_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AK620_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AK620_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AK620_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:28;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:28 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

25. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:28;

(b) fragments of the amino acid sequence of SEQ ID NO:28; and

(c) the amino acid sequence encoded by the cDNA insert of clone AK620_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

26. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:29;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:29 from nucleotide 367 to nucleotide 552;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AK650_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AK650_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AK650_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AK650_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:30;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:30 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

27. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:30;

(b) fragments of the amino acid sequence of SEQ ID NO:30; and

(c) the amino acid sequence encoded by the cDNA insert of clone AK650_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

28. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 116 to nucleotide 310;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 173 to nucleotide 310;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AM226_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AM226_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AM226_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AM226_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:33;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:33 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

29. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:33;

(b) fragments of the amino acid sequence of SEQ ID NO:33; and

(c) the amino acid sequence encoded by the cDNA insert of clone AM226_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

30. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:35;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:35 from nucleotide 281 to nucleotide 418;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:35 from nucleotide 353 to nucleotide 418;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AR417_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AR417_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AR417_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AR417_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:36;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:36 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

31. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:36;

(b) fragments of the amino acid sequence of SEQ ID NO:36; and

(c) the amino acid sequence encoded by the cDNA insert of clone AR417_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

32. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:38;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:38 from nucleotide 496 to nucleotide 583;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:38 from nucleotide 565 to nucleotide 583;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AU43_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AU43_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AU43_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AU43_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:39;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:39 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

33. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:39;

(b) fragments of the amino acid sequence of SEQ ID NO:39; and

(c) the amino acid sequence encoded by the cDNA insert of clone AU43_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

34. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:41;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:41 from nucleotide 55 to nucleotide 405;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:41 from nucleotide 148 to nucleotide 405;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone AW60_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone AW60_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AW60_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AW60_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:42;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:42 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

35. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:42;

(b) fragments of the amino acid sequence of SEQ ID NO:42; and

(c) the amino acid sequence encoded by the cDNA insert of clone AW60_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

36. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:44;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:44 from nucleotide 337 to nucleotide 525;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:44 from nucleotide 406 to nucleotide 525;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BA176_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BA176_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BA176_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BA176_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:45;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:45 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

37. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:45;

(b) fragments of the amino acid sequence of SEQ ID NO:45; and

(c) the amino acid sequence encoded by the cDNA insert of clone BA176_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

38. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:47;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:47 from nucleotide 536 to nucleotide 628;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BD140_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BD140_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BD140_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BD140_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:48;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:48 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

39. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:48;

(b) fragments of the amino acid sequence of SEQ ID NO:48; and

(c) the amino acid sequence encoded by the cDNA insert of clone BD140_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

40. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:50;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:50 from nucleotide 303 to nucleotide 617;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:50 from nucleotide 345 to nucleotide 617;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BD407_1i deposited under accession number ATCC 98190;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BD407_1i deposited under accession number ATCC 98190;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BD407_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BD407_1i deposited under accession number ATCC 98190;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:51;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:51 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above; and

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above.

41. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:51;

(b) the amino acid sequence of SEQ ID NO:51 from amino acid 1 to amino acid 32;

(c) fragments of the amino acid sequence of SEQ ID NO:51; and

(d) the amino acid sequence encoded by the cDNA insert of clone BD407_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

42. A composition comprising an isolated protein encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:52;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:52 from nucleotide 178 to nucleotide 534;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone BF290_1i deposited under accession number ATCC 98190;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone BF290_1i deposited under accession number ATCC 98190;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BF290_1i deposited under accession number ATCC 98190;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BF290_1i deposited under accession number ATCC 98190;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:53;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:53 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above; and

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above.

43. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

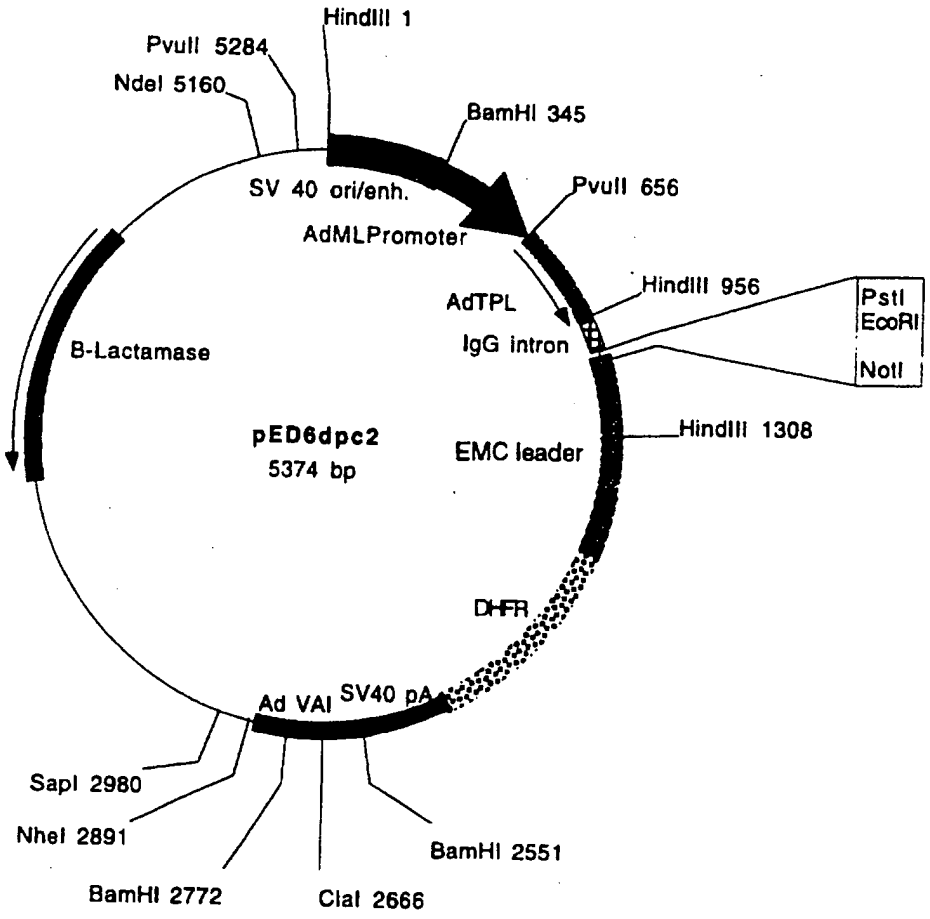
(a) the amino acid sequence of SEQ ID NO:53;

(b) fragments of the amino acid sequence of SEQ ID NO:53; and

(c) the amino acid sequence encoded by the cDNA insert of clone BF290_1i deposited under accession number ATCC 98190;

the protein being substantially free from other mammalian proteins.

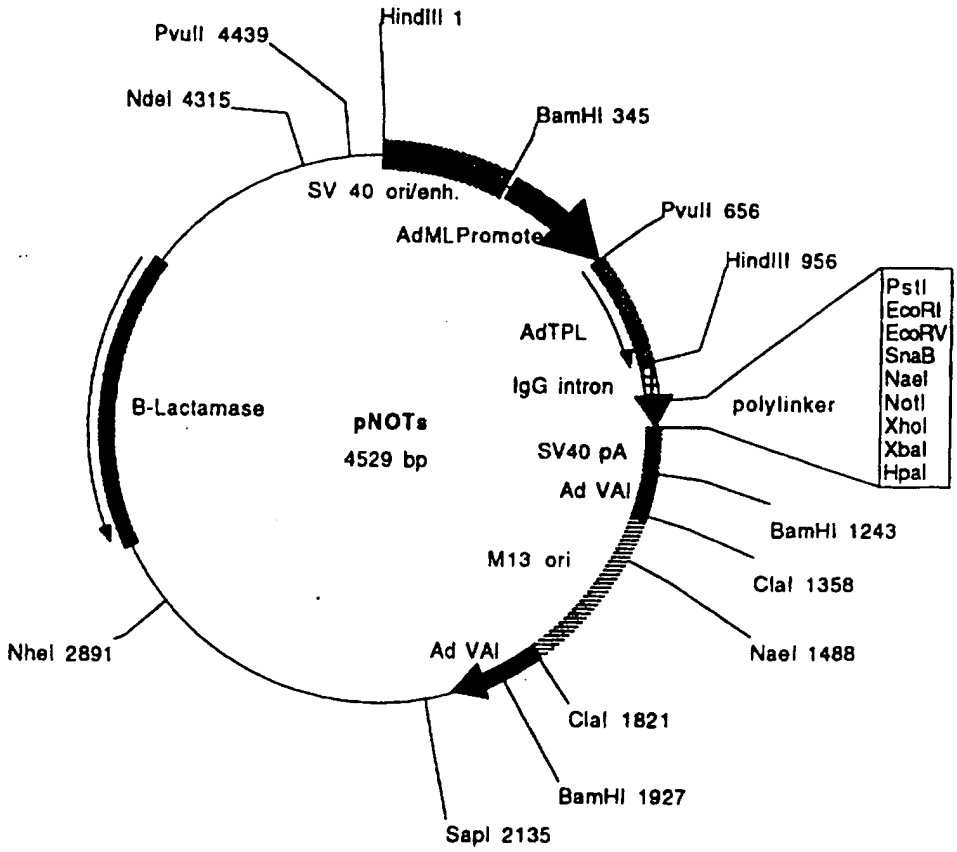
# FIGURE 1A




**Plasmid name:** pED6dpc2
**Plasmid size:** 5374 bp

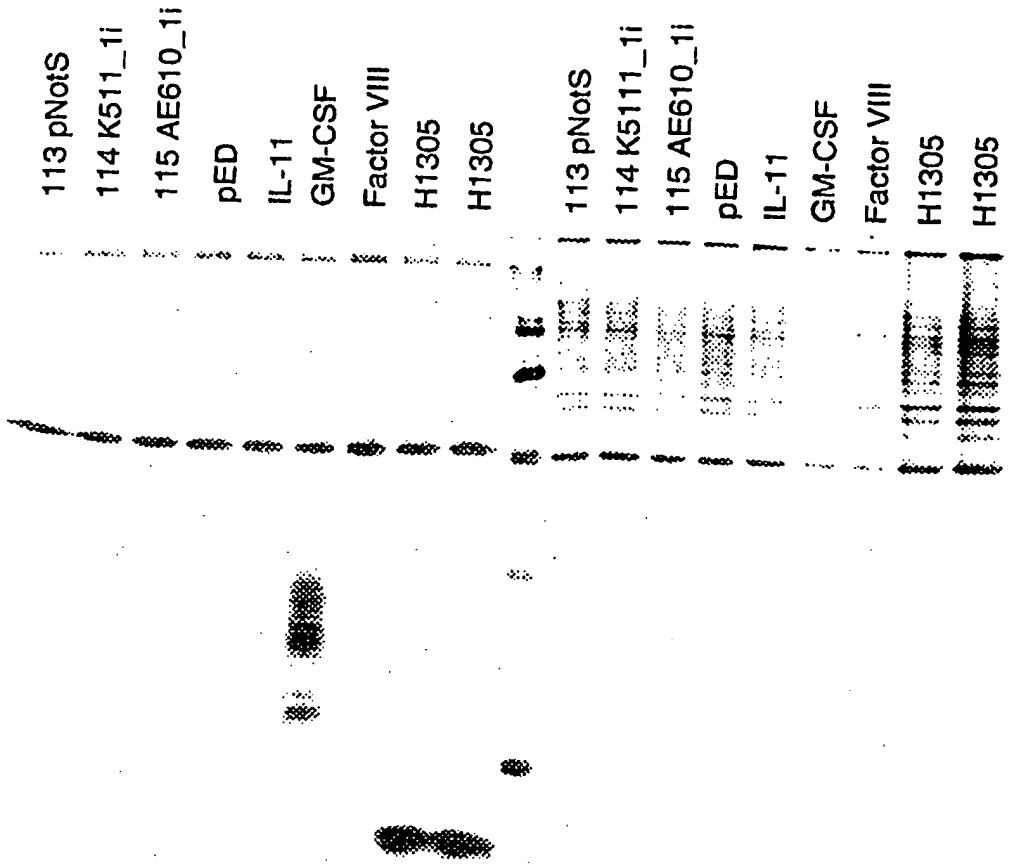
**C mments/References:** pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

# FIGURE 1B




**Plasmid name:** pNOTs
**Plasmid size:** 4529 bp

**Comments/References:** pNOTs is a d rivative of pMT2 (Kaufman et al,1989. Mol.Cell.Biol.9:1741-1750). DHFR was deleted and a n w polylinker was inserted between EcoRI and HpaI. M13 rigin of replication was inserted in the ClaI site. SST cDNAs are cloned between EcoRI and NotI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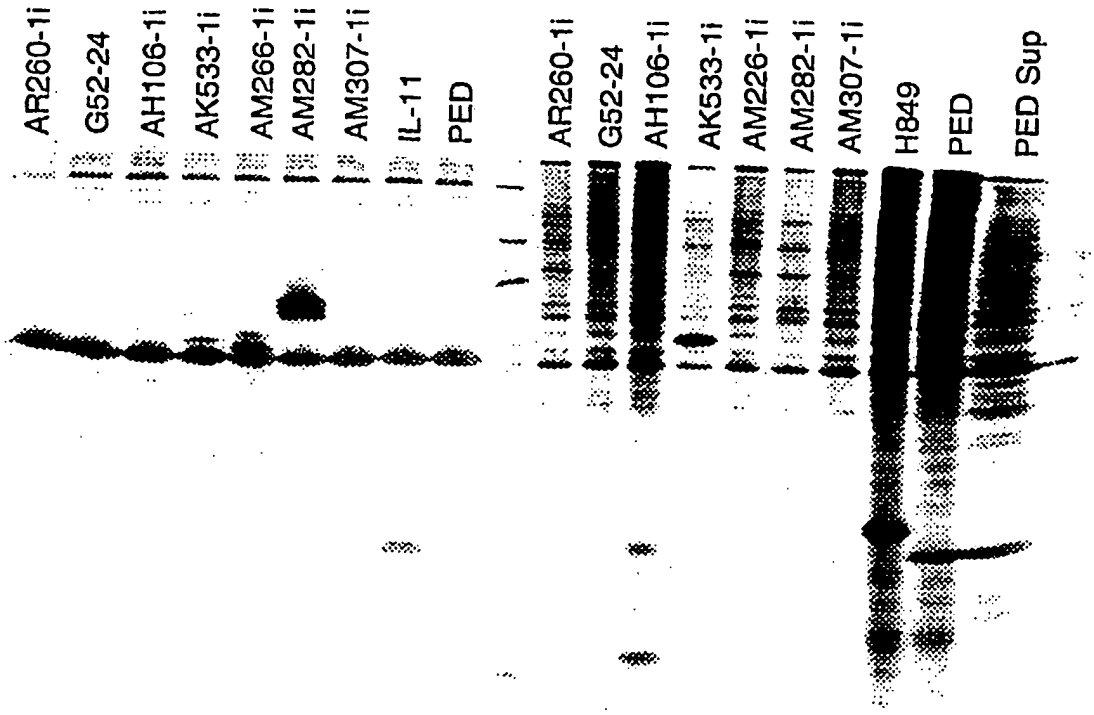
114 K511_1i
115 AE610_1i
pED
IL-11
GM-CSF
Factor VIII
H1305
H1305
113 pNotS
114 K5111_1i
115 AE610_1i
pED
IL-11
GM-CSF
Factor VIII
H1305
H1305

Fig. 2


AR260-1i
G52-24
AH106-1i
AK533-1i
AM266-1i
AM282-1i
AM307-1i
IL-11
PED
AR260-1i
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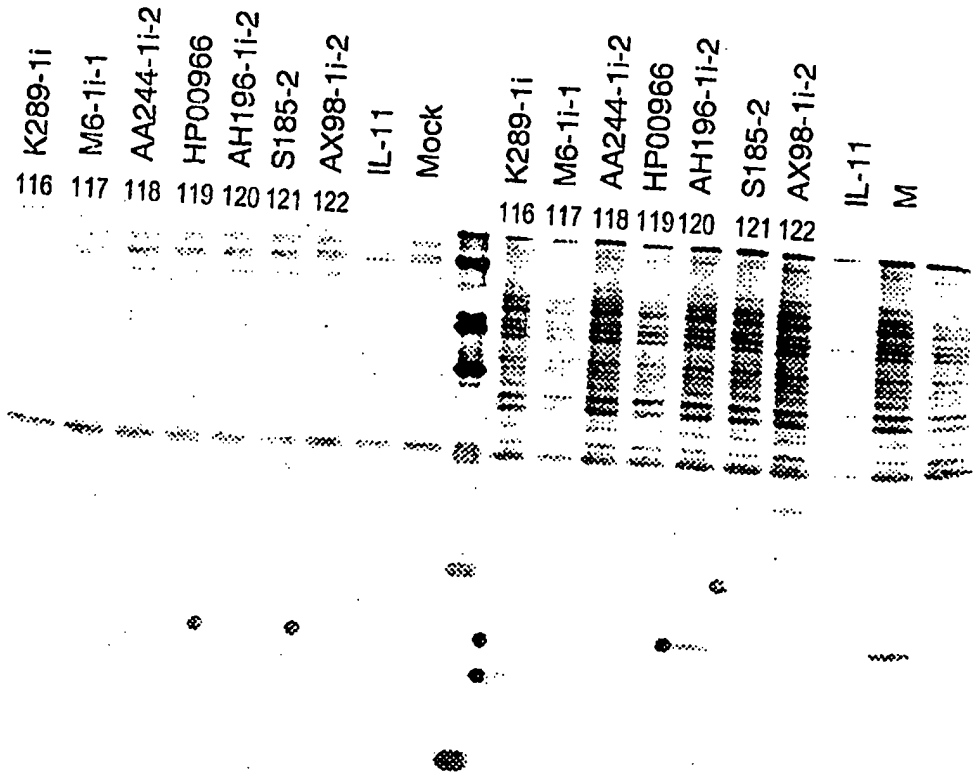
AM282-1i
AM307-1i
H849
PED
PED Sup

Fig. 3


K289-1i
116
M6-1i-1
117
AA244-1i-2
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HP00966
119
AH196-1i-2
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S185-2
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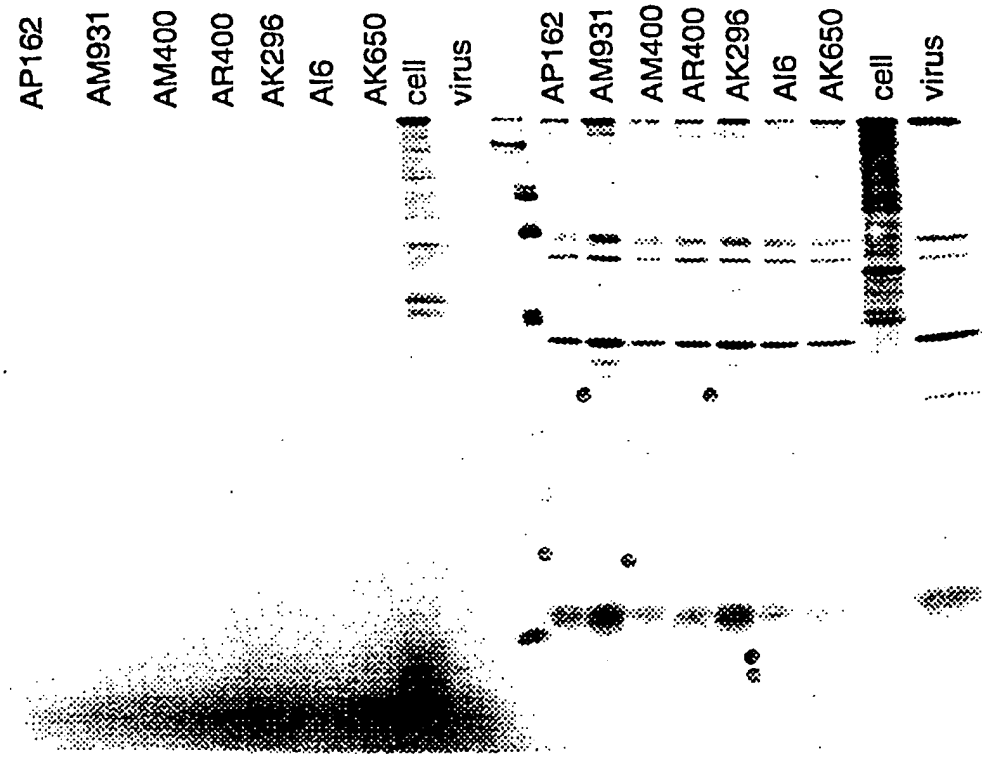
AX98-1i-2
122
IL-11
Mock
K289-1i
116
M6-1i-1
117
AA244-1i-2
118
HP00966
119
AH196-1i-2
120
S185-2
121
AX98-1i-2
122
IL-11
M

Fig. 4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AP162
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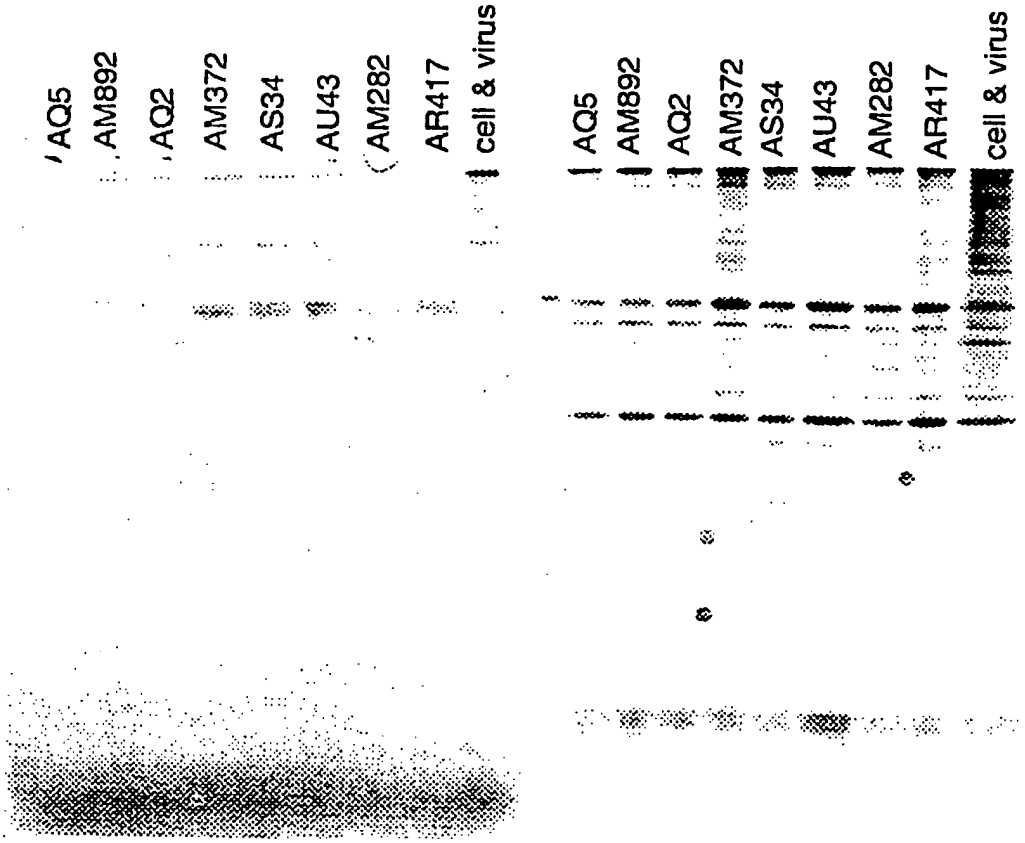
cell
virus

Fig. 5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AM372
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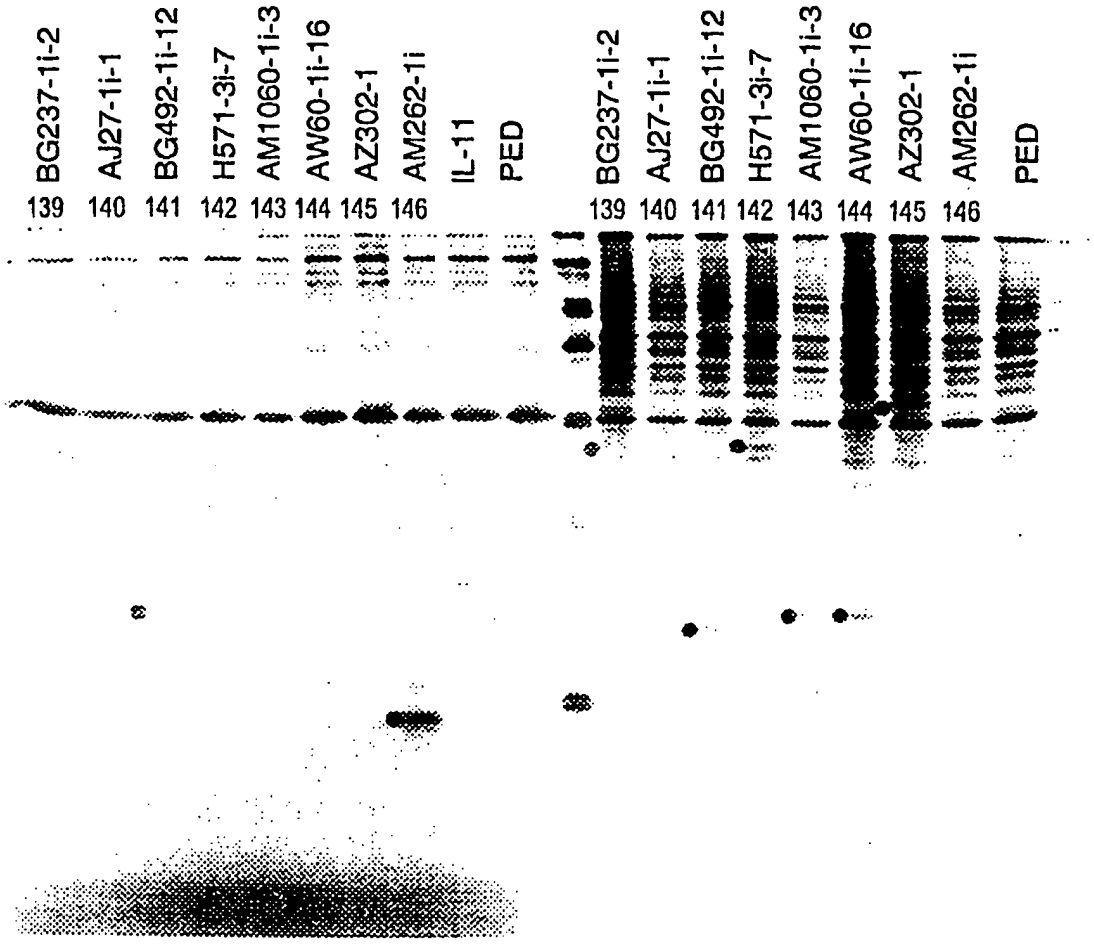
AU43
AM282
AR417
cell & virus

Fig. 6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AM262-1i
IL-11
PED
139 140 141 142 143 144 145 146
BG237-1i-2
AJ27-1i-1
BG492-1i-12
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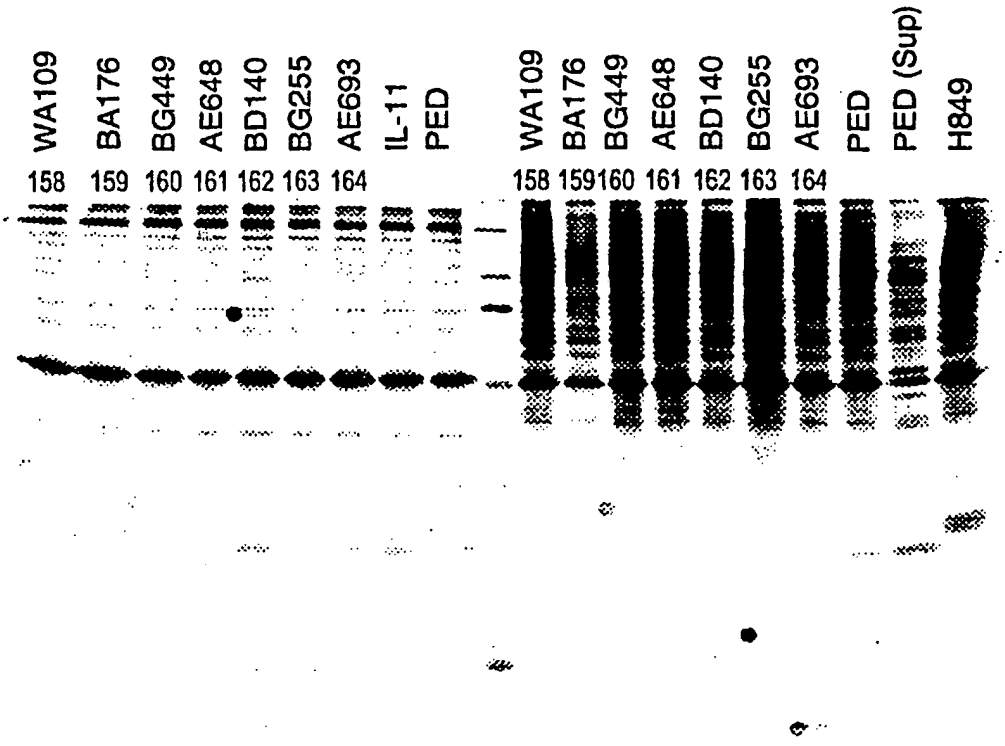
139 140 141 142 143 144 145 146

Fig. 7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WA109
BA176
BG449
AE648
BD140
BG255
AE693
PED
PED (Sup)
H849
158
159
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162
163
164

Fig. 8

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be

readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell

interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

## ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical

composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunolgobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically

acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition

of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 µg to about 100 mg (preferably about 0.1µg to about 10 mg, more preferably about 0.1 µg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated

that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular

application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorbtion of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.